IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Stoughton *et al.*
Serial No.:	09/038,894
Conf. No.:	8909
Cust. No.:	20985
Filed:	March 11, 1998
For:	*METHODS OF DIAGNOSIS AND TRIAGE USING CELL ACTIVATION MEASURES*
Art Unit:	1654
Examiner:	Meller, M.

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11/02/2004
Date

Stephanie Seidman

BRIEF ON APPEAL

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02 FC:2255 1040.00 OP

(1) REAL PARTY IN INTEREST

The instant application is assigned to The Regents of the University of California, The Scripps Research Institute, and to Cell Activation, Inc.

(2) RELATED APPLICATIONS ON APPEAL OR IN INTERFERENCE

There are no related applications on appeal or in interference.

(3) STATUS OF CLAIMS

Claims 10-18, 32-36, 38, 41 and 42 are presently pending in this application. All claims are finally rejected.

(4) STATUS OF THE AMENDMENTS

This is an appeal from the final rejection of claims 10-18, 32-36, 38, 41 and 42, mailed January 12, 2004. All amendments have been entered.

(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

The following is a brief discussion of subject matter of the application to aid in appreciating the claimed subject matter. As discussed in detail below, the instant application and claims are directed to methods in which the level of cell activation is employed as a therapeutic intervention point, a therapeutic indicator and/or a diagnostic/prognostic marker Figures 1-3 in the application provide an exemplary and schematic description of the use of cell activation as a marker and therapeutic intervention point.

Cell Activation

Cells in microcirculation can be encountered in a relatively quiescent state and in various stages of activation. As stated on page 16, line 21, - page 17, line 4, of the application, for example:

> Cell activation refers to changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces. For example, adhesion molecules and villi attach macrophage and monocytes to endothelium. Macrophage and monocytes may then infiltrate into tissue outside the blood vessel beginning the development of atherosclerosis, venous insufficiency ulcers an diabetic retinopathy.

Thus cell activation is a parameter that is marked by physical and metabolic changes in white blood cells. The level thereof can be assessed using assays that detect such physical and/or metabolic changes in white blood cells.

A certain level of cell activation is a normal physiological response that is essential for survival. Through the inappropriate stimulation of various defense strategies involving inflammatory cells and the immune system, an animal often is responsible for its own demise. The first inflammatory cells to be upregulated in these conditions are polymorphonucleated (PMN) cells, or neutrophils. These cells, which include 60% of the circulating pool of leukocytes in humans, constitute a formidable line of defense against invading pathogens. When activated, they produce a number of cytotoxic components including oxygen free radicals and proteases designed to destroy and degrade invading bacteria.

When unregulated, secreted leukocyte products also can kill cells in the body and destroy tissue. Inappropriate activation of such immune cells is implicated in the pathology of many disease processes (see, Section B of the application, for example). Cardiovascular complications, such as myocardial infarction, venous ulceration and ischæmia/reperfusion injury are associated with an activation of cells in circulation. Activated neutrophils release a number of toxic substances including free radicals, proteases and their products that kill cells and ultimately destroy tissues. Neutrophils also release cytokines and other inflammatory substances, resulting in the recruitment of additional neutrophils and activated cells, further propagating inflammation and injury. Thus, as described and shown throughout the application (see, e.g., Section B, starting on page 20 and Figs. 1-3), inappropriate or excessive activation is related to certain acute and chronic diseases and poor disease and treatment outcomes. For example, Section B, page 20 et seq., of the application, describes that the activation of cells is linked to a variety of diseases, including myocardial infarction, hemorrhagic shock, general health and subclinical compromise thereof, diabetes, hypertension, and venous insufficiency as well as an array of other disorders.

Claims on Appeal and some of the supporting disclosure in the application

Claims on appeal

The claims capture this subject matter and methods. In particular, the claims in this application are directed to methods of preventing diseases, improving treatment outcome and reducing risk by assessing cell activation levels, and, if elevated, administering cell activation lowering therapy to lower the levels of cell activation.

(a) Independent claim 10 and dependent claims

In particular, **claim 10** is directed to a method of improving treatment outcome or reducing risk of treatment for a disease or condition in a subject with a disease or condition. The method, as claimed, includes the steps of:

assessing treatment options for the disease or condition by measuring cell activation levels in a subject with the disease or condition; and, if cell activation levels are elevated,

administering activation lowering therapy prior to commencing treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment.

Dependent claim 11 specifies that cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation. Claim 12 specifies that the disease or condition treated is selected from cardiovascular disease, inflammatory disease, trauma, autoimmune diseases, arthritis, diabetes and diabetic complications, stroke, ischemia, Alzheimer's disease. Claim 13 specifies that the treatment being assessed is surgery, treatment of unstable angina or treatment for trauma. Claim 14 specifies that activation lowering therapy comprises administering a protease inhibitor, dialysis, alterations in lifestyle to reduce stress, or alterations in diet. Claim 15 specifies that the protease inhibitor is a serine protease inhibitor and claim 16 specifies that the protease inhibitor is selected from among α_1-proteinase inhibitor (α_1-antitrypsin), α_2-macroglobin, inter-α_1-trypsin inhibitor, and α_1-antichymotrypsin. Claim 17 specifies that the disease or condition is selected from among myocardial infarction, stroke, hemorrhagic shock, diabetic retinopathy, diabetes and venous insufficiency. Claim 18 specifies that the protease inhibitor in claim 14 is 6-amidino-2-naphthyl p-guanidinobenzoate dimethanesulfonate (Futhan) or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof.

(b) Independent claim 32 and claims dependent thereon

Claim 32 is directed to a method for preventing a disease or disorder or reducing risk of having a poor outcome from treatment. The method includes the steps of:

assessing cell activation in a subject; and, if elevated,

administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of a treatment of a disease or disorder.

Claim 33 specifies that the activation lowering therapy comprises modifications in diet and/or lifestyle. Claim 34 specifies that activation lowering therapy comprises administration of a protease inhibitor. Claim 35 specifies that the protease inhibitor is a serine protease inhibitor and claim 36 specifies that the protease inhibitor is selected from

among α1-proteinase inhibitor (α1-antitrypsin), α2-macroglobin, inter-α1-trypsin inhibitor, and α1-antichymotrypsin. Claim 38 specifies that activation lowering therapy comprises dialysis. Claim 41 specifies that the protease inhibitor in the method of claim 35 is 6-amidino-2-naphthyl p-guanidino-benzoate dimethanesulfonate or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof. Claim 42 recites that cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation.

Exemplary disclosure in the application describing the claimed subject matter

It is shown in the instant application and reflected in the claims (discussed below) that the level of cell activation serves as a therapeutic intervention point and as a diagnostic and prognostic indicator in diseased and in healthy individuals. As shown in the application cellular activation, including neutrophil activation, can be used as an indicator of therapeutic outcome (prognosticator) and also a as therapeutic target and as a diagnostic indicator.

If cell activation levels can be lowered, then a variety of diseases, such as stroke and other ischemic events, whose onset is exacerbated or mediated by cell activation, can be prevented or treatment outcomes improved. By lowering cell activation levels, the exacerbating or mediating forces of a disease or disorder can be counteracted in advance of a disease or disorder occurring or prior to or simultaneous with other therapy. In doing so, some or many or most of the devastating consequences of such disease or disorder are averted or reduced or the risk of poor treatment outcomes is reduced.

Figures 1-3 in the application depict the role of cell activation in some exemplary disease states and conditions and therapeutic and diagnostic/prognostic intervention points. FIGURE 1 depicts a summary of the relation of cell activation to disease showing that cell activation plays a central role, for example, in cardiovascular diseases and in the immune response and shows that it responds to lifestyle factors, as well as trauma, ischemia, infection; it initiates or potentiates atherosclerosis; causes poor outcome in trauma, shock, MI; participates in a disease positive feedback loop; and is governed by circulating plasma factors. FIGURE 2 schematically depicts cell activation diagnostic and therapy points (ARDS refers to Adult Respiratory Distress Syndrome, and MOF refers Multiple Organ

Failure). FIGURE 3 shows l therapeutic intervention points; 3a) depicts intervention downstream from activation; and 3b) depicts intervention before activation by attacking activating factors as a way of reducing risk or preventing disease or lessening the severity of a disease.

Thus, among what is provided in the instant application is the use of cell activation for diagnosis and therapeutic intervention (see, e.g., Figure 2, which sets forth the paradigm for the methods of assessing treatment options). Methods for measuring cell activation are known and are outlined in the application. The application also teaches that cell activation levels can be used as a diagnostic indicator in healthy individuals as part of routine screening and in individuals with a variety of disorders to aid in assessing treatment options and predicting outcome.

Cell activation is pivotal in disease outcomes, trauma outcomes, and general long term good health, measurement of activation levels should be performed in healthy individuals who present no disorders. As described in the application, identification of healthy individuals with elevated levels of activated cells, permits early identification of at-risk individuals and permits early intervention, in chronic and also in acute diseases. As shown in Figure 2, in a seemingly healthy patient activation levels are measured. If low, then no treatment or changes in lifestyle are recommended. If the levels are elevated ,then tests to determine the presence of subclinical infection or other cell activating condition are performed. If those tests are negative, then lifestyle and diet should be examined, and if, necessary, modified. If diet is good, and lifestyle is generally good and stress-free, then activating lowering therapy can be instituted.

Testing cell activation levels pre-surgery, particularly elective surgery, (or prior to administration of treatments for diseases in subjects with diseases) can be used to assess the likelihood of complications from the treatment, such as surgery or organ transplant rejection. For example, for pre-operative subjects, if high levels of cell activation that are not the result of infection are found, then surgery should be postponed and activation lowering therapy considered. Similarly, in unstable angina, the levels of cell activation are indicative of the risk of a cardiovascular event. Thus, if levels are high, activation lowering therapy and/or more aggressive treatment should be pursued. In trauma situations, the level of cell activation

can aid in selecting treatment protocol and timing thereof. High levels of activation are associated with ARDS and MOF in the emergency room. Activation lowering therapy should reduce the risk thereof.

Thus, in general, if a high level of cell activation is observed, then activation lowering therapy should be administered prior to (or in conjunction with) further treatment. Activation lowering therapy includes administration of known pharmaceuticals, such as aspirin and cardiovascular medications, dialysis and other such treatments, lifestyle changes, and as described in this application administration of protease inhibitors, such as futhan..

Assessing levels of cell activation

The instant application provides diagnostic/prognostic and therapeutic methods in which the level of cellular activation is assessed. Cellular activation is assessed by detecting changes is metabolic properties or physical properties of white blood cells indicative of activation. For example, cell activation can be assessed using known assays for free radical production, such as defined by the nitroblue tetrazolium test and lucigenin-enhanced chemiluminescence, and/or assays for actin polymerization, such as defined by the pseudopod formation test. Assays can be performed on whole blood or on leukocytes or other suitable samples and indicate, individually or in combination, the level of cell activation. Page 25, line 27,- page 26, line sets for exemplary tests for detecting cell activation:

> In practicing the method, one or more tests for cell activation would be performed. These tests, discussed and exemplified below in more detail below and include tests that assess indicators of activation, such as changes in shape and free radical production. For example cell morphological changes may be quantified with direct microscopic examination, with or without fluorescent staining of F-Actin filaments present in pseudopods, or with fluorescence activated cell sorting techniques. Superoxide anion production can be detected and quantified using chemiluminescence generating reagents, such as luminol, isoluminol and lucigenin, that quantitatively react therewith. Free radicals can be assessed by NBT (nitroblue tetrazolium). Activation can be assessed by various immunoassays that detect surface adhesion molecules, such as CD11, CD18 and L-selectin and others. Other indicators of activation include expression of certain factors, such as interleukin and TNF-α, which can be measured by known immunoassays.
>
> Activation can also be assessed by sampling plasma and determining whether it activates cells, such as endothelial cell cultures. Plasma can be tested for clastogenic activity by standard methods. Although there is a high correlation between the different cell activation assay measures, it is likely that

there will be different combinations of indicators which are most informative in any situation. For example, plasma activator levels might be high but circulating activated neutrophil counts low due to sequestration of the activated cells in the microcirculation. Also, genetic, age, and environmental differences between patients will complicate the interpretation of the assays. Clinical tests are in preparation to relate statistically cell activation measures to disease outcomes, to find the formulas which are invariant to patient differences, and to establish the best predictive procedures and activation lowering therapies in different situations. The measurement of cell activation and circulating plasma factors also serves as an effective tool to evaluate the effectiveness of new interventions prior to execution of full-scale clinical trials. Drug candidates thereby may be rejected, or patient populations enriched for more favorable response to the candidate drug.

Page 35, line 15 - page 36, line 13 describes cell activation assays:

Rates of free radical production in whole blood can be measured using phenol red (Pick et al. (1980) J. Immunol. Methods 38:161-170) or other dye forming reagents (U.S. Patent No. 5,518,891). Intracellular radical production may be measured with nitroblue tetrazolium (NBT) reduction or chemiluminescence (Cheung et al. (1984) Aust. J. Expt. Biol. Med. Sci. 62:403) assays. Radical production in whole blood or plasma may be measured electrochemically, and mRNA expression of specific genes can be quantitated, for example, using Northern blots or DNA microarrays.

Expression of adhesion molecules such as CD11b, CD18, and of L-Selectin can be quantitated via flow cytometry, while cytokines and chemokines, such as interleukins and TNF-a can be quantitated with immunoassays.

Cell morphological changes may be quantified with direct microscopic examination, with or without fluorescent staining of F-Actin filaments present in pseudopods, or with fluorescence activated cell sorting techniques.

Blood plasma is known to carry cell activation factors in response to specific events. Plasma from I/R episodes including MI (Chang et al. (1992) Biorheology 29:549-561) and hemorrhagic shock (Elgebaly et al. (1992) J. of Thoracic and Cardiovascular Surgery 103(5):952-959; Paterson et al. (1993) Am. Vasc. Surg. 7(1):68-75; Barroso-Aranda et al. (1995) J. Cardiov Pharmacology 25(Suppl 2):S23-S29) activates neutrophils, as does plasma from smokers' blood (Pitzer et al. (1996) Biorheology 33(1):45-58). Patient blood samples can be applied to standard donor cells and the response of the donor cells used as a measure of the potency of the circulating activating factors in the patient blood.

Page 46, line 17, - page 47, line 20 - describes Other assays and development of other assays:

Donor cells or cell cultures responding to patient blood plasma samples can be used show cell activation behavior, clastogenic (mutagenic) activity,

apoptotic potential, effects on intercellular junctions such as relevant to the blood-brain barrier, and general gene transcriptional effects.

Once circulating plasma factors are isolated and identified, antibodies to these factors will provide specific assays.

Another method in which patient plasma assayed for its ability to activate neutrophil as an indication of the presence of cell activation is provided herein (see, Example 6). It can be used in the classical fashion; that is, fresh patient blood is centrifuged and the plasma measured for superoxide formation. In another embodiment, control plasma from healthy individuals can be used as a vehicle to test activation of different substances, even other patient plasma. This latter method provides neutrophils in autogolous plasma and obviates the need for large amounts of patient plasma. As little as 100 µl of plasma (and possible less using the new smaller volume configuration) can be measured for its ability to activate otherwise quiescent neutrophils. This method can give accurate results in as little as 1 hour (10 minutes centrifugation, 10 minutes setup and 40 minutes of measurement). Because the number of neutrophils in spun plasma is much less than that of isolated neutrophils in autologous plasma, the relative levels of chemiluminescence are likewise attenuated. In normal (control) plasma, all values thus far (>100 experiments with more than 5 different donors) have had a maximum response of between 1500 and 6000 counts/sec in a time frame of 20-50 minutes. The normal range is approximately 3000+/-500 counts/sec in approximately 40 minutes. This can be modified by donor illness, antibiotics, and more interestingly, ingestion of fatty diet.

These assays alone or in combination can be used to identify other factors and/or to assess levels of cell activation, which will be related to disease outcomes and can be used to support useful therapeutic decisions. Other assays for measuring cell activation levels in patient samples, include any cell activation known to those of skill in the art, and particularly those exemplified herein.

In the Examples, Example 2 exemplifies a variety of assays for cell activation - oxidative burst, actin polymerization, nitroblue tetrazolium assay; peroxide production, pseudopod formation, Example 3 -describes Lipid Peroxidation as indicator of cell activation and exemplifies Methods for Measuring Lipid Peroxidation, plasma per oxide assay, and Example 6 - chemiluminescence assay for superoxide production

Cell Activation lowering therapies

The results of the assays are used to support therapeutic decisions. These decisions (see, *e.g.*, Figure 2) include further testing for infectious agents; anti-oxidant or anti-adhesion therapy; postponement and optimal re-scheduling of high- risk surgeries; classifying

susceptibility to and progression rates of chronic disease such as diabetes, atherogenesis, and venous insufficiency; extreme interventions in trauma cases of particularly high risk; and activation-lowering therapies.

As discussed above, the pending claims are directed to methods in which cell activation level is assessed, and if elevated cell activation cell activation lowering therapy is administered to either reduce the risk of poor treatment outcome, to prevent or reduce the severity of a disease, or to reduce the risk of poor outcome of a treatment. The specification, see, *e.g.*, page 19, lines 11-15 defines activation lowering therapy:

> As used herein, activation lowering therapy (A.L.T.) refers to any means in which the level of activated cells is lowered. Such means include lifestyle and dietary changes, drug therapy, such as aspirin, pentoxifylline, Daflon 500 (a flavonoid), anti-inflammatories, inderal, heparin, coumadin, Futhan and other protease inhibitors.

. Activation lowering therapy methods include any method that lowers activation. Methods for lowering activation are known in the art and some of these as well as new methods, such as administration of protease inhibitors, are described in the application. Cell activation lowering therapy includes, alterations in lifestyle, such as stress management, exercise and dietary changes, administration of drugs, such as heart medications, aspirin. As shown in the application, administration of protease inhibitors, such as Futhan (nafamostat mesilate, which is 6-amidino-2-naphthyl p-guanidinobenzoate dimethanesulfonate, also lowers cell activation level. Cell activation lowering therapy is described throughout the application. For example, at in Section F, page 36, line 14, -page 38, line 31, the specification provides details of exemplary therapies, reproduced as follows:

> Tests for activation would be empty without constructive responses to the information gleaned in the tests. Responses can take the form of adjustments to lifestyle and diet, such as increased exercise and lowered fat intake, postponement of scheduled surgery, anti-oxidant and activation-lowering drug therapy, or antagonists to circulating plasma factors. Examples of therapeutic decision trees are given in Figure 2.
>
> Nominally healthy patients with high activation, for example, can be counseled to adjust lifestyle and diet, or given an anti-oxidant (Stephens et al. (1996) The Lancet 347:781-786) or a relatively harmless activation-lowering therapy such as aspirin (Ridker et al. (1997) New England J. Medicine 336(14):973-979). High-risk surgery patients with high activation levels could postpone surgery or be given an activation-

lowering therapy. An example of an existing protocol is the platelet aggregation blocker by Centocor (Reopro) given for high-risk angioplasty. Patients with unstable angina currently have choices ranging from no treatment to drug therapy to activation lowering or anti-adhesion (Husten, "Platelet receptor blockers effective for unstable angina," Internal Med. World Report, May 15, 1997) drug therapy to angioplasty to bypass surgery. These choices could be guided by the degree of cell activation observed. Unstable angina has been shown, for example, to be associated with changes in neutrophil expression of CD11b and L-Selectin (Ott et al. (1996) Circulation 94(6):1239-1246).

In some cases high activation levels will be in response to infection. If the infection is subclinical, the activation test provides a clue to its presence. If the infection is apparent for other reasons, then treating it or waiting for it to subside becomes the first step in responding to high activation in non-critical care situations.

Finally, trauma and sepsis outcomes might be indicated by the presence of circulating plasma factors and by the extremity of the observed activation levels, so that choices of extreme interventions could be selected more rationally. Serine protease inhibitors such, as Futhan are effective in animal models in vivo against hemorrhagic shock, apparently block the effects of a factor originating in the pancreas. Thus, existing protease inhibitors should be useful for treatment of hemorrhagic shock of sepsis and should serve as drug targets.

The targets for treatment will be preferably either the factors, such as those released from the pancreas, that activate cells, or proteases that participate in the activation.

Treatment with protease inhibitors

Leakage of pancreatic proteases and other factors into the blood stream, or excessive activation in the pancreas without proper endogenous inhibitor control results in life threatening events. Injury to the pancreas generally is lethal and preventing protease action at the level of the white cell is known to be important for minimizing post ischemic injury. Taken together, a drug that might be effective in preventing the generation of cell activation factors from tissues, to the extent that proteases play this role, should be therapeutic and have numerous clinical applications. This type of intervention has the potential to intervene early in the mediator/activation factor cascade and be particularly effective in minimizing post injury phenomena.

Thus, methods of treatment of disorders and conditions related to inappropriate or chronic cell activation are provided. In particular, treatment by administration of effective amounts of broad protease inhibitors, particularly serine protease inhibitors are provided. In a

> preferred embodiment, the protease inhibitor is Futhan (nafamostat mesilate, which is 6-amidino-2-naphthyl p-guanidine-benzoate dimethanesulfonate) and treatment with a pharmaceutical composition containing an effective amount of Futhan is contemplated.
>
> The protease inhibitors, such as Futhan or a similarly broad protease inhibitor, are used to treat patients in shock, suffering trauma or otherwise having compromised (i.e. individuals with activated circulating neutrophils) systems in order to minimize vessel/tissue injury. Administration is contemplated as soon as possible in the instance of a trauma or immediately prior to surgery or invasive clinical procedure in the case of compromised patients. The amounts administered (with reference to Futhan) are on the order of 0.001 to 1 mg/ml, preferably about 0.005- 0.05 mg/ml, more preferably about 0.01 mg/ml, of blood volume by any suitable means, including intravenous, intramuscular, oral and parenteral administration. In an average adult, thus, about 50 mg of Futhan per dosage is administered. Since the compound is a low molecular weight drug and can be excreted relatively rapidly the frequency of treatment may be as often as every 6 8 hours during an acute episode or as little as one dose for a surgery patient. The precise amount of particular inhibitors administered can be determined empirically and will depend upon the particular disorder treated and outcome desired.

Page 46 of the specification describes ways to identify new or other therapies. Hence, the specification describes methods for assessing cell activation, and methods for lowering levels of cell activation in great detail. All of the pending claims include the steps of assessing levels of cell activation; and, if elevated, administering cell activation lowering therapy. Claims 10 and dependents are directed to methods in which the subject has been diagnosed with disease and the method is for improving the risk or outcome of treatment for the disease or disorder. Claims 32 and dependents are directed to methods in which the subject is healthy or has a disease or disorder and cell activation therapy can prevent a disease or disorder or reduce the risk of a poor outcome of a treatment for the disease or disorder.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(a) Rejections under 35 U.S. C. § 112, first paragraph

(i) Claims 32-36, 38, 41 and 42 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly is not enabling for prevention of disease.

(ii) Claims 10-18, 32-36, 38, 41 and 42 are rejected under 35 U.S.C. §112, first paragraph for allegedly failing to provide enablement for any and all activation lowering therapies and any and all diseases or conditions and any and all methods of assessing cellular activation.

(b) Rejections under 35 U.S.C. §112, second paragraph

Claims 10-18, 32-36, 38, 41 and 42 are rejected 35 U.S.C. §112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter, because the meaning of the recitations "cell activation," "if elevated," "administering activation lowering therapy" and "preventing a disease or disorder" are allegedly unclear.

(c) Rejection under 35 U.S.C. 103(a)

Claims 10-18, 32-36, 38, 41 and 42 are rejected under 35 U.S.C. 103 as being unpatentable over Okada *et al.* ((1991) *Journal of International Medical Research 19*:234-236) (Okada 1), Okada *et al.* ((1991) *Journal of International Medical Research 19*:348-350) (Okada 2), Yanamoto *et al.* or Yonekura *et al.* in view of Gibboni *et al.*, Babcock *et al.*, and Brunck *et al.*

(7) ARGUMENTS

(a) Rejections under 35 U.S. C. § 112, first paragraph

(i) Claims 32-36, 38, 41 and 42 are rejected under are unpatentable under 35 U.S.C. § 112, first, as containing subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner continues to argue that the phrase "thereby preventing a disease" is allegedly not supported in the specification. The Examiner asserts that to prevent a disease, it must be totally eliminated and that evidence of this has not been shown on the record. This rejection is respectfully traversed.

Relevant law

In order to satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of ' 112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz*, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Claim 32 and dependents

Claim 32 is directed to a method in which the level of cell activation in a subject is assessed as a diagnostic indicator If the level is elevated, cell activation lowering therapy is administered and a disease or disorder is prevented or the risk of poor outcome of a therapy is reduced.. Claim 33 specifies that the activation lowering therapy comprises modifications in diet and/or lifestyle. Claim 34 specifies that activation lowering therapy comprises administration of a protease inhibitor. Claim 35 specifies that the protease inhibitor is a serine protease inhibitor and claim 36 specifies that the protease inhibitor is selected from among α1-proteinase inhibitor (α1-antitrypsin), α2-macroglobin, inter-α1-trypsin inhibitor, and α1-antichymotrypsin. Claim 38 specifies that activation lowering therapy comprises dialysis. Claim 41 specifies that the protease inhibitor in the method of claim 35 is 6-amidino-2-naphthyl p-guanidino-benzoate dimethanesulfonate or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof. Claim 42 recites that cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation. Hence the aspect of preventing a disease or disorder is common to all the rejected claims.

As shown in the application, lowering cell activation levels can prevent a disease or disorder or improve treatment outcome. It is contemplated in this application that cell activation levels will be monitored as part of routine physical examinations and also prior to treatment where disease has been diagnosed. When part of a routine exam, the level can be used to assess risk; when used prior to undertaking a course of therapy for a disease or disorder, administration of cell activation lowering therapy can improve the outcome of the therapy for the disease or disorder especially in the advanced stages. Claim 32 captures this concept.

Analysis

Prefatory to the arguments presented below, it is noted that the Examiner appears to be confusing prevention with cure. Stating that the disease or disorder is totally eliminated implies that the disease or disorder was already present and the subject was cured. Prevention means that a subject may never manifest a disease or disorder.

It is shown in the instant application that the level of cell activation serves as a therapeutic intervention point (and also a diagnostic indicator) in diseased and in healthy individuals. If cell activation levels can be lowered, then a variety of diseases, such as stroke and other ischemic events, whose onset is exacerbated or mediated by cell activation can be prevented or treatment outcomes improved. To prevent a disease or disorder is to counteract the exacerbating or mediating forces in anticipation or advance of the disease or disorder occurring. In doing so, all or some of the devastating consequences of such disease or disorder are averted. Preventing a stroke, for example, is not tantamount to curing a stroke. Preventing it means that all of the devastating consequences that would occur from a stroke are averted. Curing a stroke involves eliminating all of the consequences after they have occurred, such as aphasia and paralysis resulting from the stroke. Thus, prevention of the disease does not mean elimination of the disease and its root causes; prevention means to stave off a disease or disorder and the associated consequences.

First it is noted that claim 32 and its dependent claims are directed to methods for preventing a disease or disorder OR reducing the risk of a poor outcome of a treatment of a

disease or disorder. Hence, the claims are directed to alternative outcomes. Further, the claim does not require prevention of all diseases.

Second, the claims do not recite that a particular disease or disorder is prevented, only that a disease or disorder is prevented. In practicing the methods, the level of cell activation of a subject is assessed. Elevated levels are associated with the risk of developing any of a variety of diseases, including stroke, myocardial infarction and others. A subject who is tested and has elevated levels is administered or undertakes cell activation lowering therapy and thereby does not develop a disease. One could not know what diseases would have developed.

Third, as discussed in the prosecution history, the application exemplifies and demonstrates that administration of cell activation lowering therapy can prevent disease. Example 8 exemplifies prevention of a disease. The results of the experiments presented in Example 8 of the specification demonstrate that in animals pretreated with serine protease, shock and mortality was prevented. Example 8 provides detailed SAO shock models and ample evidence to support the prevention of disease by administration of activation-lowering therapy as required by the claims.

As addressed in detail in responses of record and, applying the "Wands" factors to the instant claims demonstrates that in view of the scope of the claims and data and disclosure in the specification, knowledge and level of those of skill in the art , it would not require undue experimentation to practice the claimed methods. Specifically, the observations presented in the application demonstrate that inappropriate levels of cell activation can exacerbate or mediate the onset of a disease or disorder. Thus, lowering cell activation levels can prevent the onset of a disease or disorder or reduce the severity thereof. Further, the results of experiments demonstrate prevention of disease.

Example 8 of the specification (pages 136-145) provides results of experiments employing Splanchnic Arterial Occlusion (SAO) shock models effected either by arterial clamping or by bolus injection of pancreatic homogenate. As discussed in the specification, SAO shock is a form of shock that results from reduced blood flow to the splanchnic region. The main artery supplying the splanchnic region is the superior mesenteric artery, which arises directly from the aorta and feeds the pancreas, duodenum and mesentery of the small

intestine. (Specification at page 83, lines 3-7). Reduced blood flow to the splanchnic region and mesenteric ischemia may result from "catastrophic to minimal illness, from arterial or venous occlusion to nonocclusive or low flow problems, from acute to recurrent to chronic process, from incidental end-stage circumstances to a primary disease or even an iatrogenic problem" (Williams, L., "Mesenteric Ischemia," Surgical Clinics of North America, 68(2):331-353 (1988) (enclosed herewith)). Arterial occlusion, in particular, is associated with any number of diseases and conditions including, for example, emboli, cardiovascular diseases (including myocardial infarction, stroke, atherosclerosis, hypertension), aneurysms, trauma (including burns, surgery and sepsis), lupus, arthritis, diabetes mellitus and hereditary/genetic disorders (see, e.g., Williams, Table 4).

Splanchnic arterial occlusion in rats is a well studied model of hypotension/ischemia-reperfusion injury (see, e.g., Specification at page 82, lines 30-31; Haglind, E., et al., "Graded Intestinal Vascular Obstruction: I. Description of an Experimental Shock Model in the Rat," Circ. Shock, 7:83-91 (1980)). As stated above, this type of hypotension/ischemia-reperfusion injury is associated with many different diseases and disorder. The advantage of using the rat SAO shock model is that it is a well-established model with a more circumscribed region of tissue exposed to ischemia/reperfusion compared to the more global ischemia/reperfusion that can occur with many of the above listed disease and disorders. (Specification at page 83, lines 12). As seen in cases of global ischemia/reperfusion injury resulting from, for example, hemorrhagic shock, it was found that ischemia/reperfusion in the SAO shock model results in increased cell activation. (Specification at page 88, lines 10-12). The specification specifically states:

> [t]he model of splanchnic arterial occlusion shock used in these experiments involves clamping the superior mesenteric artery as well as the celiac artery. The celiac artery supplies collateral flow to the superior splanchnic region (such as the pancreas) and ischemia to both arteries results in a much quicker and more uniformly lethal outcome than occlusion of the superior mesenteric artery alone. The third major supply vessel to the splanchnic region, the inferior mesenteric artery can also be clamped, but this results in large intestine and bowel necrosis which was unwanted in this study because of possible bacterial translocation. Clamping the superior mesenteric and celiac arteries insures almost complete ischemia to the pancreas while leaving the large intestines relatively well perfused. This model of SAO shock has been

> well studied and is quite reproducible. (Specification at page 82, lines 19-31, emphasis added)

In these experiments, animals pretreated with a serine protease such as futhan were compared with saline-pretreated control animals. The results show that performance of SAO shock protocols on saline-pretreated control animals results in uniform hypotension (shock) and death. **In animals pretreated with serine protease prior to performance of the SAO procedure, shock and mortality is completely prevented,** *i.e.*, all of the devastating consequences that occur as a result of performing the SAO procedure are averted by pre-treatment with serine protease (see, e.g., page 32, line 10-17; page 137, line 25 to page 138, line 2; and page 144, line 20). As indicated above and in the specification, shock is marked by uniform hypotension. The transient decrease in blood pressure or brief hypotension that was reported in animals pretreated with serine protease (see, e.g., page 32, lines 15-16; page 137, line 25 to page 138, line 2; and page 144, line 20) is not tantamount to shock. As specifically stated at page 32, line 15, futhan pretreated "animals did not go into shock." Thus, prevention of shock was complete. Example 8 provides ample evidence to support the prevention of disease by administration of activation lowering therapy as required by the claims. Therefore, the application shows that a disease can be prevented (i.e., never develop). in the specification and the high level of skill of those in this art, it would not require undue experimentation to practice the methods as claimed.

(ii) Claims 10-18, 32-36, 38, 41 and 42 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for treating hemorrhagic shock by assessing free radical production using phenol red and then, if levels are elevated using futhan, is allegedly not enabling for any and all activation lowering therapies and any and all diseases or conditions and any and all methods of assessing cellular activation. The Examiner reasons that the art of biotechnology is a highly unpredictable art and it would be an undue burden for one of skill in the art to test any and all activation lowering therapies and any and all diseases or conditions and any and all methods of assessing cellular activation to see if they could perform the claimed processes. This rejection is respectfully traversed.

The Examiner has provided no reasoning why the exemplary methods provided in the specification coupled with the disclosure in the application for improving treatment outcome

or reducing risk of treatment by reducing cell activation levels are not enabling with respect to the claimed subject matter. Methods for assessing cellular activation are well known to the skilled practitioner and numerous examples are disclosed in the specification. Further, the claimed methods are not directed to treatment of a specific disease, but are directed to methods of improving treatment outcome, or reducing risk of treatment for a disease, or for preventing a disease or disorder, or reducing the risk of a poor outcome of a treatment of a disease or disorder by targeting the same underlying pathology, excessive cell activation. The first paragraph of §112 does not require a specific example of everything within the scope of a broad claim.

As discussed below, the therapeutic target and diagnostic indicator is cell activation. Numerous methods and ways to lower cell activation are provided in the specification (see, discussion above regarding the claimed subject matter); these methods range from particular drugs, such as futhan, to lifestyle changes. Cell activation is a phenomenon that is known to those of skill in the art as are factors that lead to its elevation and some methods for its decrease. Prior to the instant application, however, cell activation had not been identified as a diagnostic or prognostic of disease or treatment outcome nor as a point of therapeutic intervention. Having identified it as such in the instant application, then the particulars for practicing each step in the method, from testing the levels of cell activation to methods for lowering levels, are known to those of skill in the art.

The specification provides numerous examples of different cell activation therapies and methods for identifying cell activation therapies (discussed above and also in great detail in (5), page 10-12, above). Further, the specification provides a specific definition of cell activation and, based on this definition, provides numerous methods for assessing it. Also, the specification provides detailed disclosure of how cell activation therapy is practiced and under what circumstances it may be used. As presented in detail below, although the choice of therapy may be influenced by various factors including general health of the subject and/or symptoms of a disease or disorder, the specific disease or disorder from which a subject may be suffering is of no consequence in the method. Cell activation is the target of the therapy, not any particular disease or disorder. The consequence of lowering cell activation (if levels are determined to be high) is the same for any disease or disorder; i.e., outcome of treatment

(for the disease or disorder) is improved and risks associated with treatment (for the disease or disorder) are reduced.

Further, the specification provides detailed guidance for cell activation lowering protocols (also discussed in great detail above in (5)). Again, most of these protocols, changing diet, reducing stress are not unpredictable heretofore unknown regimens. Anything that lowers cell activation is contemplated by the specification.

Relevant law

See discussion above.

The rejected claims

Claim 10 is directed to a method of improving treatment outcome or reducing risk of treatment for a disease or condition in a subject with a disease or condition. The method, as claimed, includes the steps of :

assessing treatment options for the disease or condition by measuring cell activation levels in a subject with the disease or condition; and, if cell activation levels are elevated,

administering activation lowering therapy prior to commencing treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment.

Dependent claim 11 specifies that cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation. Claim 12 specifies that the disease or condition treated is selected from cardiovascular disease, inflammatory disease, trauma, autoimmune diseases, arthritis, diabetes and diabetic complications, stroke, ischemia, Alzheimer's disease. Claim 13 specifies that the treatment being assessed is surgery, treatment of unstable angina or treatment for trauma. Claim 14 specifies that activation lowering therapy comprises administering a protease inhibitor, dialysis, alterations in lifestyle to reduce stress, or alterations in diet. Claim 15 specifies that the protease inhibitor is a serine protease inhibitor and claim 16 specifies that the protease inhibitor is selected from among α_1-proteinase inhibitor (α_1-antitrypsin), α_2-macroglobin, inter-α_1-trypsin inhibitor, and α_1-antichymotrypsin. Claim 17 specifies that the disease or condition is selected from among myocardial infarction, stroke, hemorrhagic shock, diabetic retinopathy, diabetes and venous insufficiency. Claim 18 specifies that the protease inhibitor in claim 14 is 6-amidino-2-naphthyl p-

guanidinobenzoate dimethanesulfonate (Futhan) or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof.

Claim 32 is directed to a method for preventing a disease or disorder or reducing risk of having a poor outcome from treatment. The method includes the steps of:

assessing cell activation in a subject; and, if elevated,

administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of a treatment of a disease or disorder.

Claim 33 specifies that the activation lowering therapy comprises modifications in diet and/or lifestyle. Claim 34 specifies that activation lowering therapy comprises administration of a protease inhibitor. Claim 35 specifies that the protease inhibitor is a serine protease inhibitor and claim 36 specifies that the protease inhibitor is selected from among α1-proteinase inhibitor (α1-antitrypsin), α2-macroglobin, inter-α1-trypsin inhibitor, and α1-antichymotrypsin. Claim 38 specifies that activation lowering therapy comprises dialysis. Claim 41 specifies that the protease inhibitor in the method of claim 35 is 6-amidino-2-naphthyl p-guanidino-benzoate dimethanesulfonate or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof. Claim 42 recites that cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation.

The rejection is asserted against all claims. It is apparent, however, that dependent claims specify particular methods for assessing cell activation, particular disease manifestations, and particular cell activation lowering therapies. Although Appellant does not concede that the independent claims are broader than the enabling disclosure, should it be so determined, consideration of the dependent claims, which specify various specific embodiments, each specifically disclosed and described in the specification is respectfully requested.

Analysis

There is no requirement for a specific example of everything within the scope of a broad claim. Applicant is entitled to claims that are commensurate in scope not only with what an applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the an applicant has disclosed. The

inquiry with respect to scope of enablement, is whether it would require undue experimentation to make and use what is claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation.

The specification provides detailed disclosure regarding activation lowering therapy and assays for assessing cellular activation. Indications for use of cell activation assessment and therapy are also clearly outlined in the specification and above. Based on the disclosure in the specification, it would not require undue experimentation to practice the claimed methods. .

As shown in the application the activation status of white blood cells, including neutrophils and other inflammatory cells is an important diagnostic indicator. Cell activation levels are of central importance not only in disease states, such as ischemia, infection, trauma, inflammatory diseases, but also in 'healthy' individuals. It is shown in the application that cellular activation can be used generally as a diagnostic indicator and an indicator of therapeutic outcome in individuals with a disease or disorder or in apparently healthy individuals. As shown in the application it is a therapeutic target for preventing development of diseases and also improving outcomes of treatments for disease. The instant claims are not directed to treatment of particular diseases, but to identifying the level of cell activation, and then if necessary lowering it prior to or concurrent with treatment for a particular disease. The cell activation lowering therapy is not the treatment for the disease.

Indications for use

As shown in the application, cell activation levels are significant generally, whether in good or poor health. Cell activation assays and cell activation lowering therapy can be used, respectively, as diagnostic and therapeutic procedures in a wide variety of clinical settings. It is envisioned in the application, that measurement of cell activation levels will become a routine part of a physical exam and also prior to treatment for a disease or trauma. The level of cell activation is prognostic of the risk of developing diseases and also is an indicator of the outcome of a treatment. A trauma patient with high cell activation levels, will have a poorer surgical outcome. Knowledge of the cell activation level can guide therapeutic decisions. It is these findings that are encompassed by the pending claims. The application describes them in great detail (see, e.g., section C of the specification starting at page 25 and

schematically in Figure 2). For example, cell activation measurement and therapy can be used in healthy individuals as follows:

Identification of healthy individuals with elevated levels of activated cells, permits early identification of at-risk individuals and permits early intervention, in chronic and also in acute diseases. As shown in Figure 2, in a seemingly healthy patient activation levels are measured. If low, then no treatment or changes in lifestyle are recommended. If the levels are elevated (for example, above the 20th percentile), then tests to determine the presence of subclinical infection or other cell activating condition are performed. If those tests are negative, then lifestyle and diet should be examined, and if, necessary, modified. If diet is good, and lifestyle is generally good and stress-free, then activating lowering therapy can be instituted. (Specification at bottom of page 24.)

The specification also teaches that cell activation measurement and therapy also can be important prior to surgery.

> Testing cell activation levels pre-surgery, particularly elective surgery, can be used to assess the likelihood of complications from surgery and organ transplant rejection. If high levels of cell activation that are not the result of infection are found, then, if possible, surgery should be postponed and activation lowering therapy considered. Similarly, in unstable angina, the levels of cell activation are indicative of the risk of a cardiovascular event. Thus, if levels are high, activation lowering therapy and/or more aggressive treatment should be pursued. In trauma situations, the level of cell activation can aid in selecting treatment protocol and timing thereof. High levels of activation are associated with ARDS and MOF in the emergency room. Activation lowering therapy should reduce the risk thereof. (Specification at top of page 25.)

Cell activation assessment and therapy also is important prior to or in conjunction with treatment for a disease or disorder other than surgery. For example, the specification states that inappropriate or excessive activation leads to or participates or intensifies many diseases, including, but not limited to: arthritis, atherosclerosis, acute cardiovascular incidents, Alzheimer's Disease, hypertension, diabetes, venous insufficiency, autoimmune disease and others. Cell activation is a major contributor to rejections processes in organ transplants, and to predisposition to poor outcomes in trauma and high risk surgeries. (specification at bottom of page 16 to top of page 17.) The specification specifically states that cell activation is relevant in the diagnosis and treatment of chronic disease such as

diabetes, atherogenesis, and venous insufficiency. Further, FIGURE 1 provides a summary of the relation of cell activation to disease showing that cardiovascular cell activation plays a central role in cardiovascular diseases and immune response and that it responds to lifestyle factors, as well as trauma, ischemia, infection; initiates or potentiates atherosclerosis; causes poor outcome in trauma, shock, MI; and participates in a disease positive feedback loop.

Thus, cell activation therapy is of significant importance in healthy and disease states because inappropriate levels of cell activation can generally put a subject at risk of developing disease, exacerbate an existing disease, and/or predispose a subject to poor outcomes of treatment for a disease. Although the choice of a particular methods of assessing cell activation and selecting a cell activation lowering therapy can be influenced by various factors including general health of the subject and/or symptoms of a disease or disorder, the specific disease or disorder from which a subject may be suffering is of no consequence in the claimed method. Cell activation is the target of the therapy, not any particular disease or disorder. The consequence of lowering cell activation (if levels are determined to be high) is the same for any disease or disorder; i.e., outcome of treatment (for the disease or disorder) is improved and risks associated with treatment (for the disease or disorder) are reduced. Thus, the claims are directed to treating one underlying pathology. Therefore, the claims are not broader than the enabling disclosure.

Methods for assessing cell activation

Cell activation is defined in the specification as "changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces." (Specification at page 16, lines 18-24). The specification provides many detailed assays for assessing cell activation levels based on the characteristics of cell activation described above. Further, any method known to measure one or more of the aforementioned characteristics of cell activation can be used to assess cellular activation. For example, at page 12, the specification teaches cell activation can be "assessed [by] superoxide production, such as defined by the nitroblue tetrazolium test and lucigenin-enhanced

chemiluminescence, and/or actin polymerization, such as defined by the pseudopod formation test." Starting at page 26, the specification describes a variety of exemplary cell activation assessment assays:

> The tests, discussed and exemplified below in more detail below and include tests that assess indicators of activation, such as changes in shape and free radical production. For example cell morphological changes may be quantified with direct microscopic examination, with or without fluorescent staining of F-Actin filaments present in pseudopods, or with fluorescence activated cell sorting techniques. Superoxide anion production can be detected and quantified using chemiluminescence generating reagents, such as luminol, isoluminol and lucigenin, that quantitatively react therewith. Free radicals can be assessed by NBT (nitroblue tetrazolium). Adhesion can be assessed by various immunoassays that detect surface adhesion molecules, such as CD11, CD18 and L-selectin and others. Other indicators of activation include expression of certain factors, such as interleukin and TNF-α, which can be measured by known immunoassays.
>
> Activation can also be assessed by sampling plasma and determining whether it activates cells, such as endothelial cell cultures. Plasma can be tested for clastogenic activity by standard methods. Although there is a high correlation between the different cell activation assay measures, it is likely that there will be different combinations of indicators which are most informative in any situation. For example, plasma activator levels might be high but circulating activated neutrophil counts low due to sequestration of the activated cells in the microcirculation. Also, genetic, age, and environmental differences between patients will complicate the interpretation of the assays. Clinical tests are in preparation to relate statistically cell activation measures to disease outcomes, to find the formulas which are invariant to patient differences, and to establish the best predictive procedures and activation lowering therapies in different situations. The measurement of cell activation and circulating plasma factors also serves as an effective tool to evaluate the effectiveness of new interventions prior to execution of full-scale clinical trials. Drug candidates thereby may be rejected, or patient populations enriched for more favorable response to the candidate drug.

Detailed cell activation protocols are described in Section E (page 35 et seq.) of the specification discussed above. The specification provides working examples (see, e.g., EXAMPLES 1, 2 and 6), including description of an electrode method for measuring hydrogen peroxide, which is correlated with cell activation levels.

Therefore, the specification demonstrates a variety of methods for assessing cell activation and demonstrates that such methods are known. Practice of the claimed methods

does not require any particular methods of assessing cell activation, but only selection of a method or combination thereof. Therefore, there is no basis to conclude that the specification does not enable any method of testing

Cell activation lowering therapy

Similarly, the specification provides a variety of activation lowering therapies (see section (5) above, which provides specific examples and descriptions from the specification. . The Examiner asserts that the specification does not enable the claims for any and all activation lowering therapies. It is respectfully submitted that cell activation is the therapeutic target; any suitable method for lowering cell activation can be employed.

The specification provides a variety of methods for lowering cell activation. Selection of a method will be dependent upon circumstance. For example, logic dictates that a change in lifestyle or diet is not likely to benefit a trauma patient; for such patient a more immediate treatment, such as treatment with a protease inhibitor, is warranted.

As discussed above under Indication for use, the specification provides a detailed framework for how a particular therapy may be chosen. For example, in the case of a seemingly healthy patient, if the levels are elevated (above the 50th percentile, more likely above the 20th percentile, or one standard deviation above the mean or more of a healthy control group), then tests to determine the presence of subclinical infection or other cell activating condition are performed. If those tests are negative, then lifestyle and diet should be examined, and if, necessary, modified. If diet and lifestyle are generally not stimulating cell activation, then more invasive therapy such as administration of specific cell activation lowering pharmaceuticals or procedures can be instituted.

Although it is clear that the choice of cell activation lowering therapy will likely depend on the individual circumstance as discussed above, anything that lowers cell activation can be used as a diagnostic intervention such as to prevent a disease or disorder, improve treatment outcome for a particular disease or disorder, or reduce the risk of a treatment for a particular disease or disorder. Selection of treatment is a function of the patient and circumstances.

Further, the specification lists in detail many of the different types of therapies from which to choose. As defined on page 19:

> activation lowering therapy (A.L.T.) refers to any means in which the level of activated cells is lowered. Such means include lifestyle and dietary changes, drug therapy, such as aspirin, pentoxifylline, Daflon 500 (a flavonoid), anti-inflammatories, inderal, heparin, coumadin, Futhan and other protease inhibitors.

These cell activation lowering protocols and others are described throughout the specification (see, e.g., page 13 and page 25, lines 15-20). For example, it is stated that lifestyle changes include, for example, stress management, exercise and diet. Drug therapy includes administration of known pharmaceuticals or drugs such as those listed above as well as other heart medications. Dialysis and other such procedures are also included. As indicated, the application demonstrates that protease inhibitors, such as serine proteases, including futhan, can be administered.

Further, the specification provides detailed methods for identifying compounds that lower cell activation. For example, the specification provides a pancreatic homogenate that can be used as a screening tool for identifying agents that inhibit cell activation, including protease inhibitors (see, e.g., pages 29-33; section H, top of page 46).

General comments and conclusions

Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. It would be unfair and unduly limiting to require applicant to limit the claims to the exemplified species when the specification clearly places those of skill in the art in possession of a larger genus of proteins. Therefore, it would be unfair, unduly limiting and contrary to the public policy upon which the U.S. patent laws are based to require applicant to limit the claims only to the exemplified species. See, e.g., *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts".
>
> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires

> as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require applicant to limit the claims to only the exemplified species would permit those of skill in the art to practice what is disclosed in the application, but avoid infringing such limited claims. The specification provides far more than methods treating for treating hemorrhagic shock by assessing free radical production using phenol red and then, if levels are elevated using futhan. To limit the claims are proposed by the Examiner would permit those of skill in the art to practice the claimed methods by selecting alternative cell activation assays and cell activation lowering therapies for the phenol red test and futhan administration, respectfully as taught in application Furthermore, the target of all of the methods is the same pathology, inappropriate levels of cell activation, which assumes a variety of manifestations. Limiting the methods to only one manifestation, hemorrhagic shock, of the same underlying pathology, would permit those of skill in the art to practice the disclosed methods for any other manifestation.

Furthermore, as noted above, the first paragraph of §112 does not require a specific example of everything within the scope of a claim. *In re Anderson*, 471 F.2d 1237, 176 USPQ 331, 333 (CCPA 1973). Rather, it requires only that the disclosure be sufficient to teach one of skill in the art how to make and use the claimed subject matter without undue experimentation. As discussed above, the specification describes in detail numerous methods for assessing cell activation levels and numerous cell activation lowering therapies and protocols for identifying or selecting other protocols.

Further, a patentee not only is entitled to narrow claims particularly directed to a specific embodiment, but also to broad claims that define an invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). There is no requirement for disclosure of every species within a genus. As discussed above, applicant has explicitly exemplified numerous embodiments, provides lists of manifestations, assays and treatments.

Having provided the instant application, others of skill in the art can readily practice the methods as claimed. It therefore, would be unduly limiting to limit the claims to a single

way of assessing cell activation, a single lowering therapy, and a single manifestation of elevated levels of cell activation.

Rebuttal the Examiner's Statement

The Examiner states "Applicant has only shown treating hemorrhagic shock by assessing for free radical production using phenol red and then if levels are elevated, using futhan." It should be clear from the forgoing discussion that this assertion is incorrect and is based on a misunderstanding of the claimed subject matter. To show the flaws in the Examiners specific statement, the specific steps of each independent claim are discussed in detail.

Claim 10 is directed to a method of improving treatment outcome or reducing risk of treatment by:

assessing treatment options for a disease or condition by measuring cell activation levels in a subject; and, if elevated,

administering activation lowering therapy prior to commencing further treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment. It is respectfully submitted that the method is not directed to "treating hemorrhagic shock" or any particular disease or disorder. The method is based on lowering cell activation levels. In the method of claim 10, options for treating a disease or disorder (e.g., options for treating hemorrhagic shock) are assessed by first measuring cell activation levels. As discussed above, the specification provides numerous assays, not just the phenol red assay, based on specific characteristics of cell activation described in the specification. Further, any method known to measure one or more of the aforementioned characteristics of cell activation can be used to assess cellular activation.

As described in the specification, knowing the level of cell activation is useful for guiding therapeutic decisions such as postponing surgery, choosing from more or less aggressive therapies for a disease or disorder and choosing whether or not to administer cell activation lowering therapy prior to commencing any treatment for the disease or disorder. The specification states:

> testing cell activation levels pre-surgery, particularly elective surgery, can be used to assess the likelihood of complications from surgery and organ transplant rejection. If high levels of cell activation that are not the result of

> infection are found, then surgery should be postponed and activation lowering therapy considered. Similarly, in unstable angina, the levels of cell activation are indicative of the risk of a cardiovascular event. Thus, if levels are high, activation lowering therapy and/or more aggressive treatment should be pursued. In trauma situations, the level of cell activation can aid in selecting treatment protocol and timing thereof. High levels of activation are associated with ARDS and MOF in the emergency room. Activation lowering therapy should reduce the risk thereof. (Specification at top of page 25.)

The method requires treating inappropriate cell activation level if levels are determined to be high prior to commencing any treatment for the disease (e.g., hemorrhagic shock). Thus, following the steps of the method, cell activation levels would be assessed and, if determined to be high, cell activation lowering therapy would be administered (this would entail treatment, such as futhan, to lower the elevated cell activation level). Once activation levels are lowered, a treatment for the disease or disorder (whatever that treatment might be) may be commenced. In lowering cell activation levels by administering cell activation lowering therapy prior to treating the hemorrhagic shock, the outcome of treatment for the shock will be improved or the risk associated with treatment for the shock will be reduced.

Because cell activation is a condition of the immune cells, it is clear that an inappropriate level has the potential of contributing to or exacerbating any disease or disorder and that lowering such levels will increase the likelihood that treatment of any existing disease or disorder will be improved. It has also shown that lowering cell activation in a seemingly health individual can prevent a disease or disorder. This is discussed in detail above and a specific example of how the method of claim 32 may be employed is given below. Claim 32 is directed to a method including the steps of

assessing cell activation in a subject; and, if elevated,

administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of a treatment of a disease or disorder.

As described in the application, measurement of cell activation levels can become a routine part of a physical exam. Thus, an otherwise healthy individual may have his cell activation level assessed. Identification of healthy individuals with elevated levels of activated cells, permits early identification of at-risk individuals and permits early intervention, in chronic and also in acute diseases. If activation levels are normal, then no activation lowering therapy

is recommended. If the levels are elevated (such as above the 20th percentile or other pre-selected criterion), then activating lowering therapy can be instituted. Therapy can include lifestyle and diet changes or more invasive therapy, such as drug therapy. By lowering cell activation levels, it is possible to prevent the onset of a disease or disorder or, if the elevated levels were found to be linked to a previously undetected disease or disorder, it possible to reduce the risk of a poor outcome of any subsequent treatment for the disease or disorder.

The specification demonstrates that inappropriate or excessive cell activation leads to or participates in or intensifies disease states generally. Thus, it is advantageous to assess cell activation whether a subject is in good or poor health. The specification describes a wide variety of methods of assessing cell activation, not just the phenol red assay. If levels are determined to be high, lowering cell activation is, in general beneficial. As addressed in detail above, the therapy and the specific benefit derived from the therapy will depend on the circumstance. If the subject is suffering from a disease or disorder, administering activation lowering therapy alleviates a condition (inappropriate cell activation) that would otherwise contribute to or exacerbate the disease, increasing the likelihood of a poor outcome of treatment for the disease.

Thus, the Examiner's statement that Appellant shows "treating hemorrhagic shock by assessing for free radical production using phenol red and then if levels are elevated, using futhan" is incorrect.

Conclusion

Since cell activation, as defined in the specification, is a well documented and normal physiological response of the immune system that is essential for survival and since inappropriate or excessive levels of cell activation have been found to be of significant importance generally, whether in good or poor health, it follows that assessment of cell activation levels and treatment of inappropriate levels is relevant whether a subject presents symptoms of a disease or not. And, although it is clear that the choice of cell activation lowering therapy will likely depend on the individual circumstance as discussed above, the actual disease or disorder (if one should be present) is of little consequence. It is clear that cell activation therapy is relevant anytime inappropriate levels of cell activation are found and that inappropriate levels may appear in conjunction with or as a result of any disease or

disorder that invokes an immune response or in the absence of any apparent disease or disorder. The specification provides ample guidance for identifying and choosing a particular therapy. The specification also provides ample guidance for identifying and choosing a method for assessing cellular activation. It is clear that any method of assessing cell activation or combination of methods can be employed.

(b) Rejections under 35 U.S.C. §112, second paragraph

Claims 10-18, 32-36, 38, 41 and 42 are rejected 35 U.S.C. '112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter, because the meaning of the recitations "cell activation," "if elevated," "administering activation lowering therapy" and "preventing a disease or disorder" are allegedly unclear. These rejections are addressed in turn below.

Relevant Law

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of prior art, and (3) the interpretation claims would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Claims need only "reasonably apprise those skilled in the art" of their scope and be "as precise as the subject permits." Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986), cert. den., 480 U.S. 947 (1987). The Court in Orthokinetics, Inc v. Safety Travel Chairs, Inc., 1 USPQ2d 1081 (Fed. Cir. 1986) held that a claim limitation requiring that a pediatric wheelchair part be "so dimensioned as to be insertable through the space between the doorframe of an automobile and one of the seats@ is definite. The Court stated:

> The phrase 'so dimensioned' is as accurate as the subject matter permits, automobiles being of various sizes. As long as those of ordinary skill in the art realized that the dimensions could be easily obtained, ' 112, 2d & requires nothing more. The patent law does not require that all possible lengths corresponding to the spaces in hundreds of different automobiles be listed in the patent, let alone that they be listed in the claims. 1 USPQ2d at 1088.

When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

There is no requirement for terms be defined in the claims when one of skill in the art can readily determine the meaning of the term based on the description and definitions

provided in the specification. In this respect, Appellant is entitled to be its own lexicographer [see, e.g., MPEP 2111.01 "Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage and utilize terms within the claims that are clear from a reading of the specification]. In re Hill, 73 USPQ 482 (CCPA 1947)". When an applicant has provided definitions in the specification, the claims are interpreted in light of such definition.

35 U.S.C. §112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. The claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. Shatterproof Glass Corp. v. Libby-Owens Ford Col, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir), cert dismissed, 106 S. Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular invention and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. '112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (Bendix Corp. v. United States, 600 F.2d 1364, 1369, 220 Ct. Cl. 507,514, 204 USPQ 617, 621 (1979); See, also, Carl Zeiss Stiftung v. Renishaw plc, 20 USPQ2d 1094, 1101).

Analysis

1) It is allegedly unclear what is meant by the phrase "cell activation."

It is respectfully submitted that "cell activation" is thoroughly described in the application and is well known to those of skill in the art. As defined in the application on page 16, lines 19-25, and reproduced above, cell activation refers to changes in and an upward shift in the level of interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production, release of inflammatory mediators and enzymes, pseudopod formation, a

expression of adhesion molecules and other metabolic changes. Further, as stated in the application (see, *e.g.*, pages 3-11), at the time of the effective filing date of this application and before, the skilled artisan knew that cells in microcirculation can be encountered in a relatively quiescent state and in various stages of activation. There was a large body of literature, incorporated in the instant specification by reference (see, e.g., pages 5-10), that was directed to the identification of factors responsible for cellular activation. Hence, it is clear to the skilled artisan what is meant by "cell activation" as used in the claims and defined in the specification.

2) It is allegedly unclear what is meant by the phrase "if elevated."

It is respectfully submitted that specification thoroughly describes and provides examples of what is meant by the phrase "if elevated." For example, on page 25, it is stated that cell activation is considered elevated when

> [it] is above the normal range, which can be established by sampling "healthy" people and determining the mean. In particular, individuals with activated cells in the upper 20% of levels or one standard deviation above the mean are considered candidates for activation lowering therapy.

Thus, the metes and bounds of the claims are sufficiently clear when read in light of the specification.

3) t is allegedly unclear what is meant by the phrase "administering activation lowering therapy." As discussed in detail above and defined on page 19:

> activation lowering therapy (A.L.T.) refers to any means in which the level of activated cells is lowered. Such means include lifestyle and dietary changes, drug therapy, such as aspirin, pentoxifylline, Daflon 500 (a flavonoid), anti-inflammatories, inderal, heparin, coumadin, Futhan and other protease inhibitors.

Thus, administration of therapy can be a lifestyle regimen including, for example, stress management, exercise and/or diet regimen. Administration of therapy can also mean drug therapy including, for example, administration of known pharmaceuticals or drugs such as those listed above and throughout the specification. As indicated, protease inhibitors, such as serine proteases, including futhan, can be administered. Therapy also includes other procedures, such dialysis, that are known to lower cell activation as described in the specification.

4) It is allegedly unclear what is meant by the phrase "preventing a disease or disorder."

As discussed in detail above, to prevent a disease or disorder is, not to eliminate it, but to counteract the exacerbating or mediating forces in anticipation or advance of the disease or disorder occurring. In doing so, all the devastating consequences of such disease or disorder are averted. Contrary to the Examiner's assertion, prevention is taught in the specification (see detailed discussion above).

(c) Rejection under 35 U.S.C. 103(a)

Claims 10-18, 32-36, 38, 41 and 42 are unpatentable under 35 U.S.C. §103(a) as being unpatentable over Okada *et al.* ((1991) *Journal of International Medical Research 19*:234-236) (Okada 1), Okada *et al.* ((1991) *Journal of International Medical Research 19*:348-350) (Okada 2), Yanamoto *et al.* or Yonekura *et al.* in view of Gibboni *et al.*, Babcock *et al.*, and Brunck *et al* because the claims allegedly are directed to a method of treating or preventing disorders using a protease inhibitor, and Okada 1, Okada 2, Yanamoto, and Yonekura allegedly teach administering futhan, to a patient. Gibboni and Pick are each alleged to teach that assays using phenol red are well known to be used for the measurement of hydrogen peroxide produced by cells in culture and, thus, the measurement of free radical production. Gibboni also is alleged to teach that such assays are useful for patients to check their cholesterol or glucose levels. Babcock is alleged to teach that traumas can be treated by administering compounds that scavenge free radicals. Brunck is alleged to teach that trauma, such as pancreatitis, is known to be treated by futhan.

Without providing any support from the cited references, the Examiner concludes that:

> it is clear from the record that a patient that was going to be treated for a disease would (1) have normal levels checked including, for example, blood pressure and glucose levels to rule out certain other problems; and (2) having checked glucose levels, the Examiner alleges that one would have also checked free radical production.

Again without citing any art to support his position, the Examiner states that, since such patients would normally check their glucose levels, "they would be motivated to treat their glucose overproduction if the levels were too high." Similarly, the Examiner reasons

that someone who had a trauma would want to know before that condition was treated (if it needed to be treated) by futhan whether or not free radical production had occurred . The Examiner that it would have been within the purview of the "skilled artisan" to administer the phenol red assay first to detect the free radical production and, if elevated, the measurement would indicate that treatment for the trauma would need to be performed. Such treatment would be the administration of futhan. No art that teaches or suggests a link between administration of futhan and free radical production is cited.

In addition, again without citing any art, the Examiner reasons that, if someone "has a trauma, such as pancreatitis, which is known to be treated by administering futhan," it would have been well within the purview of the "skilled artisan" to treat a trauma with futhan and to assess the treatment to see if it was necessary by using the phenol red assay since it is well known that phenol red assays are used to detect free radical production and that traumas are treated by compounds such as futhan and further that traumas are treated by compounds that scavenge free radicals. The Examiner further reasons, without citation of any art to support this position, that since traumas are treated with futhan and traumas produce free radicals, it would have been obvious to use a compound like futhan after the detection of elevated free radical production by phenol red assay, to treat the patient in an effort to reduce the free radical production.

In the Final Office Action, the Examiner states that the cited references "teach administration of futhan to a person having the claimed condition and the secondary references show that such assessment is known in the art." The Examiner concludes that:

> it would "clearly have been within the purview of the skilled artisan to do such an assessment since doctors routinely do check ups like taking blood samples and check white blood cell count which would constitute assessment of the cell activation levels.

This rejection is respectfully traversed.

As discussed below, notwithstanding the fact that the Examiner has provided no references that support his proposition that doctors measure cell activation as a prelude to treatment, the claims are not directed to methods of measuring cell activation and then treating a disease by administering futhan.

First, it is noted, that taking blood samples and checking white blood cell count does not fall within the purview of the definition of cell activation in the application and as understood by those of ordinary skill in the art. As discussed above, cell activation refers to morphological and metabolic changes exhibited by white blood cells, such changes include changes in shape and production of superoxide anions. Hence, the Examiner's reasoning in the Final Office Action, noted above, is flawed.

Second, the claims are directed to methods including the steps or checking cell activation, determining if it is elevated and if it is elevated, then administering a cell activation lowering therapy, such as futhan, *prior* to (or with) administering therapy for any disease or disorder. No reference of record singly or in any combination, teaches or suggests that cell activation levels can be employed as a point of therapeutic intervention or as a diagnostic or prognostic indicator to assess treatment outcome nor that lowering cell activation levels can improve treatment outcomes or act as a prophylactic. Furthermore, futhan is administered as a cell activation lowering therapy, not to treat the underlying disease or disorder, such as a trauma.

The claimed methods assess the level of cell activation by measuring physical and/or metabolic indicators thereof. If the levels are elevated, then treatment to lower cell activation (administration of activation lowering therapy) is initiated. The activation lowering therapy is not treatment for a particular disease. The step of administering activation lowering therapy is either prior to (or simultaneous with) treatment for a particular disease or disorder or is for reducing risk of treatment or preventing development of a disease or disorder or reducing the severity thereof. Such treatment as shown in the application can improve treatment outcome or reduce risk of treatment (claim 10), or can be prophylactic where there is no evidence of disease or can improve the risks of treatment (claim 32).

The Office Action has failed to set forth a case of *prima facie* obviousness

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 329, 933 (Fed. Cir. 1984)) and (2) the

combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 U.S.P.Q. 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" (*In re Keller*, 642 F.2d 413, 425, 208 U.S.P.Q. 871, 881 (CCPA 1981)), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983). Importantly, **all claim limitations** must be taught or suggested by the prior art to establish that claims are *prima facie* obvious. *See, e.g.*, MPEP 2143.03 and *In re Lowry*, 32 F.3d 1579, 32 U.S.P.Q.2d 1031 (Fed. Cir. 1994), citing *In re Gulack*, 703 F.2d 1381, 217 U.S.P.Q. 401 (Fed. Cir. 1983), citing *In re Royka*, 490 F.2d 981, 180 U.S.P.Q.2d 580 (CCPA 1974).

Analysis

Teachings of the Cited References and differences from the claimed methods

Okada 1 and 2

The Okada references teach that complement activation is involved in insulin-dependent diabetes mellitus and that futhan is an inhibitor of complement activation. Okada 1 teaches that futhan lowers cytotoxicity activity of sera as measured by a chromium release assay. Okada 1 does not teach assessment of cell activation nor administration of futhan to lower cell activation, nor does Okada 1 teach or suggest a method in which cell activation is assessed and, if elevated treated, as way of preventing disease, improving treatment outcome, or reducing the risk of treatment. None of the remaining references cure these deficiencies.

Okada 2 presents a study of the effect of futhan on complement activation in an adult male with insulin-dependent diabetes mellitus and provides evidence of complement activation in insulin-dependent diabetes mellitus. Okada 2 does not teach assessment of cell

activation. Further, Okada 2 does not teach or suggest administration of futhan to lower cell activation, or a method in which cell activation is assessed and, if elevated, treated as a way of preventing disease, improving treatment outcome, or reducing the risk of treatment. Thus Okada 2 does not cure any deficiencies of Okada 1.

Yanamoto *et al.*

Yanamoto *et al.* reports the therapeutic effect of futhan for treating cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Yanamoto *et al.* does not teach or suggest assessment of cell activation nor the administration of cell activation lowering therapy. The administration of Futhan in Yanamoto *et al.* is for the treatment of a particular disease, not to lower cell activation. Yanamoto *et al.* does not teach a method in which cell activation levels are assessed, and, if elevated, cell activation levels (not the underlying disease) are lowered as a way of preventing disease, improving disease treatment outcome, or reducing the risk of treatment. The reference only teaches that futhan can be used to treat cerebral vasospasm. Thus, Yanamoto *et al.* does not cure any of the deficiencies of Okada 1 and 2.

Yonekura *et al.*

Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with futhan. Yonekura *et al.* teaches that futhan inhibits proteinases of the coagulation, fibrinolysis, Kallkrein kinin and complement systems. Yonekura *et al.* does not teach or suggest assessment of cell activation nor the administration of cell activation lowering therapy if cell activation is elevated. The administration of Futhan in Yonekura *et al.* is for the treatment of a particular disease, not to lower cell activation. Yonekura *et al.* does not teach a method in which cell activation levels are assessed, and, if elevated, treated as a way of preventing disease, improving treatment outcome, or reducing the risk of treatment. The reference only teaches that futhan can be used to treat disseminated intravascular coagulation, thus, Yonekura *et al.* does not cure any of the deficiencies of Okada 1, Okada 2, and Yanamoto *et al.*

Gibboni *et al.* and Pick *et al.*

Each of Gibboni *et al.* and Pick *et al.* teaches the use of phenol red assays for the measurement of hydrogen peroxide. Pick *et al.* teaches a method for assessment of hydrogen peroxide produced by cells in culture. Pick *et al.* does not mention cell activation whatsoever, nor use of the phenol red assay to measure cell activation.

Gibboni *et al.* teaches dyes for use in detecting hydrogen peroxide in a sample. As with Pick *et al.*, Gibboni *et al.* does not mention cell activation whatsoever and, thus, does not teach or suggest the use of its dyes to measure cell activation.

Neither Gibboni *et al.* nor Pick *et al.* teaches or suggests that measurement of hydrogen peroxide can be used as a measure of cell activation. The references do not discuss treatment of any kind and, thus, do not teach or suggest administration of any treatment as a means of preventing disease, improving treatment outcome, or reducing the risk of treatment, nor do that teach or suggest a methods in which levels of cell activation are assessed, and if elevated, treatment for reduction thereof is administered. Thus, Gibboni *et al.* and Pick *et al.* do not cure any of the deficiencies of Okada 1, Okada 2, Yanamoto *et al.*, and Yonekura *et al.*

Babcock *et al.*

Babcock *et al.* teaches the use of aminosteroids for prophylaxis and treatment of ophthalmic diseases or disorders. The compounds are used to treat oxidative intraocular damage by arresting oxidative processes that cause damage to the eye.

Babcock *et al.* does not mention cell activation, nor a method in which cell activation is assessed, and if elevated, treated by administering cell activation lowering therapy to prevent disease, improve treatment outcome, or reduce the risk of treatment. The methods and compositions provided by Babcock *et al.* can be used to prevent diseases and disorders, but are not taught as administered to lower cell activation prior to (or simultaneous with) treatment for the disease. Thus, Babcock *et al.* does not cure any of the deficiencies of Okada 1, Okada 2, Yanamoto *et al.*, Yonekura *et al.*, Gibboni *et al.* or Pick *et al.* and is of very little relevance to the claimed subject matter.

Brunck *et al.*

Brunck *et al.* teaches compounds, such as futhan, that have activity as inhibitors of pancreatic trypsin, and their use in the prevention and treatment of the tissue damage or

destruction associated with pancreatitis resulting from digestive enzymes activated by trypsin. Brunck *et al.* teaches that digestive enzymes activated by trypsin are elevated in pancreatitis. Hence Brunck *et al.*, teaches the use of futhan for treatment of pancreatitis.

Brunck *et al.* does not mention cell activation. Brunck *et al.* does not teach or suggest a method in which cell activation levels are assessed, and if elevated, that therapy to lower the levels is administered before administering treatment for a disease or disorder (claims 10 and dependents) or to improve treatment outcome, or reduce the risk of treatment or as a prophylactic measure (claims 32 and dependents). As with all of the cited references the steps of assessing cell activation and administering cell activation lowering therapy (as a treatment to reduce cell activation) prior to treatment for a disease or for prophylactic purposes are not taught or suggested. None of the references teaches or suggests assessing cell activation and none suggest using its level as for diagnosis, prognosis, prophylaxis nor to reduce risks of treatment or an underlying disorder.

As discussed below, there is no motivation to have combined the teachings of Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, and Babcock, and Brunck. Notwithstanding this failure, even if there had been motivation to combine Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, and Babcock, and Brunck, the combination fails to teach to suggest all of the elements of the claimed methods. As described in more detail below, the combination of teachings of the cited does not result in the instantly claimed methods. None of the references, singly nor in any combination thereof, teaches or suggests a method in which cell activation levels are assessed, and if elevated, therapy to lower the levels is administered.

The following discussion demonstrates that:

(a) there would have been no motivation to have combined the cited references. The arguments regarding motivation to combine are not claim-specific, since such argument goes to the references, not the claims.

(b) the combination of cited references does not result in any of the claimed methods. Arguments are set forth with respect to each claim; since the claims do not stand or fall together.

(c) Also discussed is the reliance on hindsight reconstruction in setting forth the rejection. This argument is applicable to each and all claims.

(d) Specific comments of the Examiner throughout the prosecution are addressed and rebutted.

(a) There would have been no Motivation to Have Combined the Teachings of Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, Babcock, and Brunck

There would have been no motivation or suggestion from the teachings of the references that would have lead to one of ordinary skill in the art to any combination of the references absent the teachings of the instant application. Each of the references teaches a unique method, separate and complete; there is no teaching in the references related to futhan therapy that links them to the references that teach methods of measuring free radical production.

The Okada references illustrate a method of treating insulin-dependent diabetes mellitus by administering futhan. Yanamoto *et al.* reports the therapeutic effect of futhan for treating cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with futhan. There is no motivation to combine any of these methods of using futhan with the methods of Gibboni *et al.*, Pick *et al.*, Babcock *et al.* and/or Brunck *et al.*. Each of Gibboni *et al.* and Pick *et al.* teaches a method for measuring hydrogen peroxide. There is no motivation or suggestion from the references to measure free radical production prior to delivering futhan. The Okada references, Yanamoto *et al.* and Yonekura *et al.* teach treatments of diseases with futhan, but they do not teach or suggest the use of futhan for cell activation lowering therapy. None teaches or suggests measurement of cell activation levels, and none teach or suggests lowering cell activation if cell activation levels are elevated.

Brunck *et al.* teaches that futhan inhibits trypsin and, thus, futhan can be administered to treat pancreatitis caused by trypsin damage. As with Okada (1), Okada (2), Yanamoto *et al.* and Yonekura *et al.*, there is no suggestion for using futhan for cell activation lowering therapy nor that futhan lowers cell activation. Further, Brunck does not teach or suggest the measurement of cell activation levels and administering futhan to lower such levels. Nor does Brunck teach or suggest the administration of futhan in conjunction with or prior to

treatment for a disease to improve treatment outcome, or to reduce the risk of treatment. There also is no suggestion of a method of prophylaxis .

Babcock *et al.* teaches a method for treating a particular disease, not a precursor (high levels of cell activation) to a disease. Babcock teaches the use of aminosteroids for arresting oxidation processes in the eye for preventing or treating ophthalmic diseases or disorders, but does not suggest methods in which cell activation levels are measured prior, and if elevated, cell activation lowering therapy is administered prior to commencing therapy for a disease. There is no teaching in Babcock *et al.* that administration of aminosteroids lowers cell activation levels. Babcock *et al.* teaches their administration to arrest oxidative processes in the eye. Neither Babcock *et al.* nor any reference of record teaches or suggests that these oxidative process are, in any way, related to cell activation. Further, Babcock *et al.* does not teach or suggest a method of improving treatment outcome or reducing risk of treatment, by first measuring cell activation levels, and, if they are elevated administering cell activation lowering therapy. Babcock *et al.*, as the Okada references Yanamoto *et al.*, Yonekura *et al.*, and Brunck *et al.*, is directed to methods of treating particular diseases. None of the references teaches or suggests methods of treating cell activation as a precursor to treatment for disease or as a prophylactic measure.

Gibboni *et al.* and Pick *et al.* do not teach or suggest the measurement of cell activation as part of a therapeutic protocol, and none suggest such combination. Gibboni *et al.* and Pick *et al.* are each directed to particular assays to measure hydrogen peroxide.

Thus, there would have been no motivation from the teachings of the references to have combined the teachings of Okada (1), Okada (2), Yanamoto *et al.* Yonekura *et al.* and/or Brunck *et al.* with those of Gibboni *et al.* and/or Pick *et al.* These references do not teach that futhan can be used to lower cell activation. Gibboni *et al.* and/or Pick *et al.* do not teach or suggest that their assess can be used to assess cell activation.

(b) The Combination of Teachings of Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, Babcock, and Brunck Fails to Result in the Claimed Methods

Notwithstanding that there would have been no motivation to have combined the teachings of the cited references, the combination of teachings of the references does not result in the claimed methods. None of the references teaches or suggests a method that

includes the steps of assessing cell activation levels, and, if elevated administering cell activation lowering therapy prior to (or with) administering treatment for a disease or disorder (claim 10 and dependents) or prophylactic ally or to reduce risk of treatment (claim 32 and dependents) .

Yanamoto teaches treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage with futhan; Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with futhan; Babcock *et al.* teaches the use of aminosteroids for arresting oxidation processes and prophylaxis and treatment of ophthalmic diseases or disorders; Brunck *et al.* teaches compounds that have activity against trypsin, such as futhan, for the treatment of the tissue damage or destruction associated with pancreatitis. None teach measuring the level of cell activation nor administering futhan or any treatment for lowering cell activation.

These references fail to teach or suggest a method of improving treatment outcome or reducing risk of treatment, by assessing treatment options for a disease or condition by measuring cell activation levels in a subject; and, if elevated, administering activation lowering therapy prior to commencing or with further treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment; nor a method of prophylaxis, diagnosis and treatment by assessing cell activation; and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

None of these references, singly nor in any combination, teaches a step of measuring cell activation levels to assess whether they are elevated, nor a method in which if cell activation levels are elevated, initiating cell activation lower therapy. In all references in which futhan is administered, it is administered as the treatment for a disease, not for cell activation lowering therapy, and certainly not following assessment of cell activation to determine if the level is elevated.

Neither Gibboni *et al.* nor Pick *et al.* cures these deficiencies. Each of Gibboni *et al.* and Pick *et al.* teaches an assay for measuring hydrogen peroxide. Neither reference teaches or suggests assessing the levels of cell activation to determine if they are elevated nor administering cell activation lowering therapy if the levels are elevated. Neither reference,

singly or in combination, teaches or suggests administering treatment to lower cell activation, if cell activation levels are high. The steps of the claimed methods are either prior or with treatment for a particular disease (claim 10), or are prophylactic (claim 32) where there is no evidence of disease or as way to improve the risks of poor outcome of treatment (claim 32). Therefore, the combination of teachings of the references does not result in the instantly claimed methods.

(i) Claim 10 and claims dependent thereon

No combination of teachings of any or all of the cited references teaches or suggests a method (claim 10) of improving treatment outcome or reducing risk of treatment by assessing treatment options by:

1) measuring cell activation levels in a subject; and

2) if cell activation levels are elevated, administering activation lowering therapy **prior** to commencing any treatment for the disease or condition. The cell activation therapy, such as administration of futhan, is **not** the treatment for a disease or condition, but refers to therapy to be administered **that is distinct from the treatment of a disease or condition**.

(a) Claim 11

Dependent claim 11 specifies that cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation. None of the cited references teaches or suggests any of these assays for assessing cell activation. Thus, for the reasons discussed above with respect to claim 10 and further because none of the cited references teaches such assays, the combination of teachings of the cited references fails to result in the method of this claim.

(b) Claim 12

Dependent Claim 12 specifies that the disease or condition treated is selected from cardiovascular disease, inflammatory disease, trauma, autoimmune diseases, arthritis, diabetes and diabetic complications, stroke, ischemia, Alzheimer's disease. None of the cited references teaches or suggests measuring cell activation in a subject having any of these diseases nor treating such subject, if cell activation levels are elevated, to lower cell activation levels in addition to treating them for any of these diseases. Thus, for the reasons discussed above with respect to claim 10 and further because none of the cited references

teaches assessing cell activation levels subjects with any of cardiovascular disease, inflammatory disease, trauma, autoimmune diseases, arthritis, diabetes and diabetic complications, stroke, ischemia or Alzheimer's disease nor treating such subjects with cell activation lowering therapy, the combination of teachings of the cited references fails to result in the method of this claim

(c) Claim 13

Claim 13 specifies that the treatment being assessed is surgery, treatment of unstable angina or treatment for trauma. As with claim 12, none of the . None of the cited references teaches or suggests measuring cell activation in a subject having any of these diseases nor treating such subject, if cell activation levels are elevated, to lower cell activation levels in addition to treating them for any of these conditions. Therefore, as with claims 10-12, the combination of teachings of the cited references fails to result in the method of this claim.

(d) Claim 14

Claim 14 specifies that activation lowering therapy comprises administering a protease inhibitor, dialysis, alterations in lifestyle to reduce stress, or alterations in diet. None of the cited references teaches or suggests dialysis, alterations in lifestyle to reduce stress, or alterations in diet for any purpose. Furthermore, none of the cited references teaches or suggests that any protease inhibitor can be used to lower cell activation levels.

Therefore, for the reasons discussed above with respect to claims 10-13, and because no reference of record suggests that a protease inhibitor lowers the levels of cell activation, the combination of teachings of the cited references fails to result in the method of this claim.

(e) Claim 15

Claim 15 specifies that the protease inhibitor is a serine protease inhibitor and claim 16 specifies that the protease inhibitor is selected from among α_1-proteinase inhibitor (α_1-antitrypsin), α_2-macroglobin, inter-α_1-trypsin inhibitor, and α_1-antichymotrypsin. As with claim 14, none of the cited references teaches or suggests that any protease inhibitor can be used to lower cell activation levels. Therefore, for the reasons discussed above with respect to claims 10-14, the combination of teachings of the cited references fails to result in the method of this claim.

(f) Claim 17

Claim 17 specifies that the disease or condition is selected from among myocardial infarction, stroke, hemorrhagic shock, diabetic retinopathy, diabetes and venous insufficiency. None of the cited references teaches or suggests measuring cell activation in a subject having any of these diseases nor treating such subject, if cell activation levels are elevated, to lower cell activation levels in addition to treating them for any of these diseases. Thus, for the reasons discussed above with respect to claim 10, and further because none of the cited references teaches assessing cell activation levels in subjects with any of myocardial infarction, stroke, hemorrhagic shock, diabetic retinopathy, diabetes and venous insufficiency, nor treating such subjects with cell activation lowering therapy, the combination of teachings of the cited references fails to result in the method of this claim.

(g) Claim 18

Claim 18 specifies that the protease inhibitor in claim 14 is 6-amidino-2-naphthyl p-guanidinobenzoate dimethanesulfonate (futhan) or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof. Furthermore, none of the cited references teaches or suggests that any protease inhibitor, including futhan can be used to lower cell activation levels. Therefore, for the reasons discussed above with respect to claims 10-14, the combination of teachings of the cited references fails to result in the method of this claim.

(ii) Independent claim 32 and claims dependent thereon

(a) Claim 32

Claim 32 is directed to a method for preventing a disease or disorder or reducing risk of having a poor outcome from treatment. The method includes the steps of:

assessing cell activation in a subject; and, if elevated,

administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of a treatment of a disease or disorder.

As discussed above, none of the cited references, singly or in any combination thereof, teaches or suggests a method in which cell activation is assessed to determine whether or not it is elevated. None, suggests administration of cell activation lowering therapy. Further, none of the cited references, singly or in any combination thereof, teaches or suggests

administration of cell activation therapy to any subject in order to prevent any disease or disorder nor to reduce the risk of a poor outcome of a treatment.

Thus, no combination of teachings of any or all of the cited references teaches or suggests a method a (claim 32), of assessing cell activation; and, if elevated, administering activation lowering therapy, to thereby prevent a disease or disorder or reduce the risk of a poor outcome of treatment of a disease or disorder.

(b) Claim 33

Claim 33 specifies that the activation lowering therapy comprises modifications in diet and/or lifestyle. None of the cited references teaches or suggests alterations in diet or lifestyle for any purpose. Therefore, for the reasons discussed above with respect to claim 32 and because no reference of record suggests alterations in diet or lifestyle for any purpose, the combination of teachings of the cited references fails to result in the method of this claim.

(c) Claim 34

Claim 34 specifies that activation lowering therapy comprises administration of a protease inhibitor. None of the cited references teaches or suggests that any protease inhibitor can be used to lower cell activation levels. Therefore, for the reasons discussed above with respect to claim 32, the combination of teachings of the cited references fails to result in the method of this claim.

(d) Claim 35

Claim 35 specifies that the protease inhibitor is a serine protease inhibitor. None of the cited references teaches or suggests that any protease inhibitor can be used to lower cell activation levels. Therefore, for the reasons discussed above with respect to claims 32 and 33, the combination of teachings of the cited references fails to result in the method of this claim.

(e) Claim 36

Claim 36 specifies that the protease inhibitor is selected from among α1-proteinase inhibitor (α1-antitrypsin), α2-macroglobin, inter-α1-trypsin inhibitor, and α1-antichymotrypsin. None of the cited references teaches or suggests that any protease inhibitor can be used to lower cell activation levels. Therefore, for the reasons discussed above with respect to claims

32-35, the combination of teachings of the cited references fails to result in the method of this claim.

(f) Claim 38

Claim 38 specifies that activation lowering therapy comprises dialysis. None of the cited references teaches or suggests any method that includes cell activation lowering therapy, and none mention dialysis for any purpose. . None of the cited references teaches or suggests that any protease inhibitor can be used to lower cell activation levels. Therefore, for the reasons discussed above with respect to claims 32-36 the combination of teachings of the cited references fails to result in the method of this

(g) Claim 41

Claim 41 specifies that the protease inhibitor in the method of claim 35 is 6-amidino-2-naphthyl p-guanidino-benzoate dimethanesulfonate or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof. None of the cited references teaches or suggests that any protease inhibitor can be used to lower cell activation levels. Therefore, for the reasons discussed above with respect to claims 32-35, the combination of teachings of the cited references fails to result in the method of this claim.

(h) Claim 42

Claim 42 recites that cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation. None of the cited references teaches or suggests any of these assays for assessing cell activation. Thus, for the reasons discussed above with respect to claim 32 and further because none of the cited references teaches such assays, the combination of teachings of the cited references fails to result in the method of this claim.

Conclusion

Thus, not only was there not motivation to have combined the teachings of the cited references, the combination of teachings of the cited references does not result in any of the instantly claimed methods. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

(c) The Combination of teachings References to result in any claimed method is based on the impermissible use of Hindsight

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983).

As noted, teachings of the combination of references do not result in the instantly claimed methods. For the combination of teachings to result in the methods as claimed, requires use of the teachings of the application at issue. To produce the claimed methods, requires picking and choosing portions of methods taught in the cited references, combining them as claimed in the application and adding teachings of the instant application. Hence claimed methods are not prima facie obvious because the combination of teachings of the references does not result in the instantly claimed methods absent use of the instant application in combination therewith.

For example, it is inappropriate for the Examiner to pick the part of the methods of Gibboni *et al.* and/or Pick *et al.*, that relies on the measurement of hydrogen peroxide and conclude that because methods of measuring hydrogen peroxide are known, that it would have been obvious to have used them to assess whether cell activation levels are elevated. None of the cited references suggests assessing cell activation levels and none suggests using such an assays to assess whether cell activation levels are elevated. The Examiner has, therefore, relied on what is taught by the instant application.

Furthermore, it is inappropriate for the Examiner to pick the part of the method of Babcock *et al.*, that relies on treating ophthalmic diseases with compounds that scavenge free radicals and the portion of Brunck that relies on treating pancreatitis with futhan to arrive at the conclusion that, "since traumas are treated with futhan and traumas produce free radicals, it would have been obvious to use a compound like futhan after the detection of elevated free radical production, to treat that patient with futhan in an effort to reduce the free radical production." None of the references teaches detecting elevated free radical production as a

means to assess cell activation, and then, if elevated, administering treatment to reduce cell activation. None teaches or suggests that futhan lowers cell activation levels. Therefore, the Examiner has improperly relied on hindsight in setting forth the rejection, has failed to recognize the actual elements of the claimed methods, and has failed to set forth a *prima facie* case of obviousness.

(d) Rebuttal to specific arguments raised by the Examiner in the Office Actions

1) In response to Appellant's arguments filed October 28, 2002, in which Appellant asserted that none of the references singly or in combination taught or suggested the elements of assessing cell activation and administering cell activation lowering therapy prior to treatment for a disease or for prophylactic purposes. In response the Examiner , without providing any support from the cited references, urged that it is clear from the record that a patient who was going to be treated for a disease would have normal levels checked including, for example, blood pressure and glucose levels to rule out certain other problems. Having checked glucose levels, the Examiner alleges that one have also would have checked free radical production.

There is no teaching or suggestion in any cited reference that supports the Examiner's reasoning. Glucose overproduction is neither a measure nor indicator of free radical levels in a patient or cell activation. Having checked glucose levels, there is no cited reference that teaches or suggests that one would then check free radical production as a measure of cell activation. If the Examiner is referring to the teachings of Gibboni *et al.*, it is respectfully submitted that he has misunderstood its teaching. Gibboni *et al.* teaches dyes that are useful for detecting compounds which form hydrogen peroxide as a result of their interaction with an enzyme, such as glucose in the presence of glucose peroxidase, or cholesterol in the presence of cholesterol oxidase. The hydrogen peroxide produced by the interaction of the compound with enzyme reacts with the dye allowing quantitation of the compound (i.e., glucose or cholesterol). The hydrogen peroxide measured is the hydrogen peroxide produced by reaction of the compound with an enzyme, it is not a measure of free radical levels in a patient or patient sample. Gibboni *et al.* provides no correlation between glucose levels and free radical levels in a patient. The teachings of Gibboni *et al.* do not suggest a method in

which cell activation levels are assessed at any time, including prior to or with treatment for a disease or as a prophylactic.

As discussed throughout the prosecution, the Examiner cannot take official notice of facts outside the record that are not capable of instant and unquestionable demonstration. MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well- known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..
>
> The Examiner states the one of ordinary skill in the art having checked glucose levels would have checked cell activation levels. There is no art of record that provides such teaching or suggestion. The Examiner has not cited any art that demonstrates the one of ordinary skill in the art having checked glucose levels would have checked free radical levels.

MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

In this instance, there is no evidence that knowledge that evidences that one of ordinary skill in the art would check free radicals prior to treatment for diabetes or any other disease nor as prophylactic in healthy subjects. This area of technology is of an esoteric nature, since it is to be used by those in the medical profession. For esoteric technology, MPEP 2144.03 states:

> ("[A]ssertions of technical facts in areas of esoteric technology must always be supported by citation of some reference work" and "allegations concerning specific `knowledge' of the prior art, which might be peculiar to a particular art should also be supported." Furthermore the applicant must be given the opportunity to challenge the correctness of such assertions and allegations. **"The facts so noticed serve to `fill the gaps' which might exist in the evidentiary showing" and should not comprise the principle evidence upon which a rejection is based.**). See also In re Barr, 444 F.2d 588, 170 USPQ 330 (CCPA 1971) (scientific journal references were not used as a basis for taking judicial notice that controverted phrases were art-recognized because the court was not sure that the meaning of the term at issue was indisputable among reasonable men); and In re Eynde, 480 F.2d 1364, 1370, 178 USPQ 470, 474 (CCPA 1973) ("The facts constituting the state of the art

> are normally subject to the possibility of rational disagreement among reasonable men and are not amenable to the taking of [judicial] notice.").

In this instance, the Examiner taking of judicial notice appears to provide an element of the claims, which is not taught or suggested by any art of record. There is no art of record that suggests that cell activation levels are predictive of anything, and none that suggest methods that include measurement thereof as a prelude to treatment or prophylactically. The Examiner is taking judicial notice of allegations important to the rejection and combining them with a references that do not suggest the claimed element or methods.

In this instance, a reference or references supporting assertions by the Examiner should be provided. No references of record teaches or suggests that such tests are ever performed, that treatment options are evaluated based upon the level of cell activation nor that futhan or any compound or regimen should be used prior to therapy for a disease or condition or as a way to improve treatment outcome or reduce risk of treatment or as a prophylactic.

2) The Examiner states that someone who had a trauma would want to know before that condition was treated (if it needed to be treated) by futhan whether or not free radical production had occurred. Again, there is no teaching in any of the cited references nor any art of record that suggests that "someone who had a trauma would want to know [their level of cell activation] before initiating treatment. Again, there is no teaching or suggestion in the cited art for treatment of elevated levels of cell activation, nor for the use of futhan or any compound or regimen therefor. There is nothing of record to support this conclusion; this is based on teachings in the instant application. Furthermore, treatment by futhan in the context of the instant claims is not for treatment of the trauma, but is for lowering cell activation before (or during) treatment for the trauma.

3) It is alleged that the ordinarily skilled artisan would have been motivated to use a compound like futhan after the detection of elevated free radical production by phenol red assay, to treat the patient in an effort to reduce the free radical production. It is respectfully submitted that the claims require administration of treatment to lower cell activation not free radical production. Free radical production simply provides a means of assessing cell activation, it is not the specific target of therapeutic intervention although it

may necessarily be reduced upon reducing cell activation. Further, there are no teachings or suggestions in any of the cited references to measure free radical levels as a means to assess cell activation prior to administering therapy for a particular disease or condition, nor as a prophylactic measure nor to reduce the risk of a poor outcome to a treatment, nor is there any suggestion for using futhan to lower cell activation. Furthermore, there is no teaching in any of the references that futhan provides cell activation lowering therapy.

4) The Examiner concludes that it would have been within the purview of the "skilled artisan" to administer the phenol red assay first to detect the free radical production and, if elevated, the measurement would indicate that treatment for the trauma would need to be performed. Such treatment would be the administration of futhan.

First it is noted, that this is **not** what is claimed. According to the instant claims, cell activation levels are assessed, and if the levels are high, then cell activation lowering therapy is commenced. All of this is separate from the treatment for the disease or condition, such as trauma. In fact, if levels are elevated, treatment for the trauma or disease, if possible, might be **delayed** to permit a reduction in the cell activation levels.

Administration of futhan for treatment of trauma, is not what is claimed. The methods involve assessing cell activation levels, and if elevated, administering cell activation-lowering therapy **prior** to performing treatment, or administering cell activation-lowering therapy and selecting an alternative treatment. The cell activation lowering therapy is **not** the treatment for the disease (*i.e.*, trauma), but to lower cell activation levels which contribute to poor treatment outcomes and risks of certain diseases. Futhan, if selected as the cell activation lowering therapy, is administered, not to treat the traumatic injury or disease, but to lower the risks of treatment, such as surgery, for the trauma or disease. There is no suggestion in any cited reference to lower levels of cell activation by treatment with futhan or any treatment or regimen; there is no suggestion to assess such levels.

Second, it is noted that the standard for obviousness, is the level of skill of the ordinarily skilled artisan, not the skilled artisan. Second, it is not relevant whether something is within the level of skill of the ordinarily skilled artisan, if the cited references do not teach or suggest the act that is within the level of skill.

5) The Examiner states that it would (1) be routine to assess treatment by administering a phenol red assay because it is well known that phenol red assays are used to detect free radical production, 2) treat trauma with futhan because pancreatitis is well known to be treated by futhan, and 3) use a compound like futhan after the detection of elevated free radical production in an effort to reduce the free radical production because traumas are treated with futhan and traumas produce free radicals. No support for these allegations is provided. Again, the Examiner is reminded that of MPEP 2144.03, which requires documentation to support such statements. As noted above, the instant claims are not directed to methods of treating pancreatitis, but to methods in which levels of cell activation are assessed, and if elevated, are reduced by treatment, not for the underlying disease, but to reduce levels of cell activation.

There is no basis provided for the Examiner's assertion that it would have been obvious to use a compound like futhan after the detection of elevated free radical production in an effort to reduce the free radical production because traumas are treated with futhan and traumas produce free radicals. The Examiner has provided no reference that teaches or suggests administration of futhan following measurement of cell activation, nor for the purpose of lowering cell activation.

Even if the ordinarily skilled artisan had been motivated to use futhan to reduce free radical production, this is not what is claimed. As noted, the claimed methods require the step of assessing cell activation levels prior to administering therapy for a disease, and then based upon the assessment, administering therapy to lower cell activation levels, not for treatment of any particular disease, and then either with the cell activation lowering therapy or afterward treating the disease.

None of the cited references, singly or in any combination thereof, teaches or suggests a method of improving treatment outcome or the risk of treatment or for prophylaxis by assessing the level of cell activation, determining if the level is high, and then administering cell activation lowering therapy. Thus, the cited references, singly or in any combination thereof, fail to teach or suggest the elements of the claims.

6) The Examiner states that Gibboni *et al.* teaches that phenol red assays are useful for patients to check their cholesterol or glucose levels. This may be correct; there,

however, is no suggestion in this or any reference for assessing levels of cell activation. Gibboni *et al.* teaches methods for detecting hydrogen peroxide in a sample; Pick *et al.* teaches a method for assessment of hydrogen peroxide produced by cells in culture, and is of no relevance to the instant claims. Furthermore, the instant claims are not directed to methods for assessing glucose levels, but for assessing cell activation. Glucose levels are not a measure of cell activation.

7) The Examiner states that "a doctor routinely checks his/her patients for blood pressure, temperature, etc." and questions why Appellant thinks "that a doctor would not check his patient for any type of disorder or disease." The Examiner asserts that claim 32 is allegedly so broad that it reads on any type of "cell activation" of any condition or disease and that there is nothing specific about claim 32. The Examiner asserts that "this is a normal thing for a doctor to do."

The claim does not recite checking a patient for any disease or disorder; but rather, it recites assessing the level of cell activation. Cell activation is defined in the specification as:

> changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces." (Specification at page 16, lines 18-24).

Further, cell activation, as defined in the specification, is a documented and normal physiological response of the immune system that is essential for survival. While cell activation was known to occur, it has never before been suggested as a diagnostic indicator or therapeutic target. At the time of filing, assessment of cell activation was not a known diagnostic procedure. It also has never before been suggested to treat elevated levels of cell activation by administering cell activation lowering therapy. Thus, it was not "a normal thing for a doctor to do."

It is only by virtue of the instant specification that one of ordinary skill in the art would have been motivated to assess cell activation as a diagnostic indicator and use cell activation as an intervention point to prevent a disease or disorder, improve treatment

outcome for a particular disease or disorder, or reduce the risk of a treatment for a particular disease or disorder.

Thus, with respect to the Examiner's questions of why Appellant thinks "that a doctor would not check his patient for any type of disorder or disease" and the Examiner's assertion that "there is nothing specific about claim 32," it is respectfully submitted that the claims do not recite a step of assessing "any disease or disorder." The claims recite a step of assessing **cell activation**, a specific and measurable parameter. Such assessment is not taught or suggested by any of the cited references.

8) The Examiner states that "if one were to follow applicant's logic, then a doctor would only check his patient's temperature if the patient showed any signs already of having temperature." The Examiner asserts that "one of ordinary skill in the art also would check for "cell activation" to see if any levels of the patient had been elevated which is relative in and of itself."

As stated above, cell activation is a specific and measurable condition. None of the cited references, singly or in any combination, suggests assessing the level of cell activation. Use of cell activation levels as a diagnostic indicator and therapeutic target is presented in the instant specification for the first time. As discussed above, the level of cell activation is relevant in and of itself since inappropriate or excessive levels of cell activation have been found to be of significant importance generally, whether in good or poor health. It follows that assessment of cell activation levels and treatment of inappropriate levels is relevant whether a subject presents symptoms of a disease or not. It is only by virtue of that which Appellant has disclosed in the instant specification that one of ordinary of skill in the art would know this. The Examiner has not shown anything in the cited art or otherwise that would have lead one of ordinary skill in the art to check cell activation levels and to then administer therapy to lower the cell activation levels. The cited art does not teach that it is desirable to check levels of cell activation, nor that lowering such levels prior to treatment of a disease or disorder or for prophylaxis is desirable.

Conclusion

Therefore for all of the reasons discussed herein and throughout the prosecution history of this application, the Examiner has failed to set forth a *prima facie* case of obviousness. Not only would there have been no motivation to have combined the teachings of Okada 1, Okada 2, Yanamoto *et al.* or Yonekura *et al.* Babcock *et al.* or Brunck *et al.* with Gibboni *et al.* or Pick *et al.*, the combination of teachings of the references does not result in a method for assessing treatment options or reducing the risk of a treatment outcome or for prophylaxis, by assessing the level of cell activation in a subject, and, if elevated, treating the subject to reduce the levels of cell activation, prior to any further treatment or as a prophylactic measure.

In view of the above arguments favorable consideration and allowance of the appealed claims are respectfully requested.

* * *

Respectfully submitted,

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(8) CLAIMS APPENDIX

10. (Previously presented) A method of improving treatment outcome or reducing risk of treatment for a disease or condition, comprising:

assessing treatment options for a disease or condition by measuring cell activation levels in a subject with the disease or condition; and, if cell activation levels are elevated, administering activation lowering therapy prior to commencing treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment.

11. (Original) The method of claim 10, wherein cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation.

12. (Original) The method of claim 10, wherein the disease or condition treated is selected from cardiovascular disease, inflammatory disease, trauma, autoimmune diseases, arthritis, diabetes and diabetic complications, stroke, ischemia, Alzheimer's disease.

13. (Original) The method of claim 10, wherein the treatment being assessed is surgery, treatment of unstable angina or treatment for trauma.

14. (Original) The method of claim 10, wherein activation lowering therapy comprises administering a protease inhibitor, dialysis, alterations in lifestyle to reduce stress, or alterations in diet.

15. (Original) The method of claim 14, wherein the protease inhibitor is a serine protease inhibitor.

16. (Original) The method of claim 14, wherein the protease inhibitor is selected from among α_1-proteinase inhibitor (α_1-antitrypsin), α_2-macroglobin, inter-α_1-trypsin inhibitor, and α_1-antichymotrypsin.

17. (Previously Amended) The method of claim 10, wherein the disease or condition is selected from the group consisting of myocardial infarction, stroke, hemorrhagic shock, diabetic retinopathy, diabetes, and venous insufficiency.

18. (Original) The method of claim 14, wherein the protease inhibitor is 6-amidino-2-naphthyl p-guanidinobenzoate dimethanesulfonate or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof.

Claims 19-31 (Cancelled).

32. (Previously presented) A method, comprising:

assessing cell activation in a subject; and, if elevated,

administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of a treatment of a disease or disorder.

33. (Original) The method of claim 32, wherein activation lowering therapy comprises modifications in diet and/or lifestyle.

34. (Original) The method of claim 32, wherein activation lowering therapy comprises administration of a protease inhibitor.

35. (Original) The method of claim 34, wherein the protease inhibitor is a serine protease inhibitor.

36. (Original) The method of claim 34, wherein the protease inhibitor is selected from among α_1-proteinase inhibitor (α_1-antitrypsin), α_2-macroglobin, inter-α_1-trypsin inhibitor, and α1-antichymotrypsin.

Claim 37 (Cancelled).

38. (Original) The method of claim 32, wherein activation lowering therapy comprises dialysis.

Claims 39 and 40 (Cancelled).

41. (Previously presented) The method of claim 34, wherein the protease inhibitor is 6-amidino-2-naphthyl p-guanidinobenzoate dimethanesulfonate or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof.

42. (Previously presented) The method of claim 32, wherein cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation.

(9) EVIDENCE APPENDIX

None

(10) RELATED PROCEEDINGS APPENDIX

None